CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

Trade Name: Gleevec

Generic Name: Imatinib mesylate

Sponsor: Novartis Pharmaceutical Corporation

Approval Date: October 19, 2006

Indications: For the treatment of:

S011 - adult dermafibrosarcoma protuberans (DFSP);
S012 - adult myelodysplastic syndrome / myeloproliferative diseases (MDS/MPD);
S013 - adult Ph+ acute lymphoblastic leukemia (ALL) Monotherapy;
S014 - adult aggressive systemic mastocytosis (ASM);
S017 - adult hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S011, S012, S013, S014, S017

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

Attention: Joseph Quintavalla
Senior Regulatory Manager Drug Regulatory Affairs

Dear Mr. Quintavalla:

Please refer to your supplemental new drug applications identified below, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate) Tablets.

SUPP #	LETTER DATE	RECEIPT DATE	PROVIDES FOR THE TREATMENT OF
S011	December 16, 2005	December 19, 2005	adult dermafibrosarcoma protuberans (DFSP)
S012	December 16, 2005	December 19, 2005	adult myelodysplastic syndrome/myeloproliferative diseases (MDS/MPD)
S013	December 20, 2005	December 21, 2005	adult Ph+ acute lymphoblastic leukemia (ALL) monotherapy
S014	February 28, 2006	March 1, 2006	adult aggressive systemic mastocytosis (ASM)
S017	March 28, 2006	March 29, 2006	adult hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL)

We acknowledge receipt of your submissions dated January 24, 2006; February 6, 2006; April 7, 10, 2006; May 15, 18, and 24, 2006; and September 25, 2006.

We have completed our review of these supplemental applications, as amended. These supplemental applications are 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) and/or submitted labeling.

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 supplements NDA 21-588/S011, S012, S013, S014, S017**." Approval of this submission by FDA is not required before the labeling is used.

Submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We remind you of your postmarketing study commitments in your submission dated September 25, 2006 and amended in your e-mail communication of October 13, 2006. These commitments are listed below.

1. (for S012) To meet with the Division and the FDA Center for Devices and Radiological Health (CDRH) Office of In Vitro Diagnostics within 3 months to discuss the feasibility of a validated test kit for PDGFR gene rearrangements for patients with MDS/MPD.

2. (for S014) To meet with the Division and the FDA CDRH Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the development of a validated test kit for the detection of the D816V c-kit mutation in aggressive systemic mastocytosis.

3. (for S017) To meet with the Division and FDA CDRH Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the development of a validated test kit for the detection of the FIP 1L1-PDGFR-alpha fusion protein in HES/CEL.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

Open commitments under NDA 21-588:

Prior commitment required for accelerated approval of Gleevec for newly diagnosed pediatric CML patients (NDA 21- 588/016 submitted March 27, 2006 and approved September 27, 2006):

1. To [provide] follow up safety and efficacy information for Study 2108. Updated status reports to be submitted in March 2007 and March 2008. Provision of further long term data will be re-assessed following the submission of the March 2008 study status report and will depend on the number of patients still on study at that time.

Prior commitment required for accelerated approval of Gleevec for GIST patients (NDA 21-335/001 submitted October 15, 2001 and approved February 1, 2002):

4. Submit data from the two ongoing multicenter trials of imatinib that are testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol.

Prior commitment required for accelerated approval of Gleevec for newly diagnosed CML patients (NDA 21-335/004 submitted June 28, 2002 and approved December 20, 2002):

7. To provide interval follow-up safety and efficacy information on study 106 annually, for three additional years, and survival data and serious adverse event data thereafter for another three years. Timeline: First interval report submitted on December 22, 2003 and to be submitted annually thereafter until January 2009.

We also remind you of your postmarketing commitments which are not a condition of accelerated approval.

Prior commitments which are not a condition of accelerated approval of Gleevec for CML patients (NDA 21-335/000 submitted February 1, 2001 and approved May 10, 2001):

11. To conduct the appropriate study to assess the potential drug interaction between Gleevec and a substrate of CYP2D6 and to submit the final study report.

14. To evaluate the etiology and treatment of the fluid retention syndrome associated with imatinib treatment.

    We refer to your submission of September 5, 2006 regarding this commitment. This submission is under review by FDA.

Prior commitment which is not a condition of accelerated approval of Gleevec for GIST patients (NDA 21-335/001 submitted October 15, 2001 and approved February 1, 2002):

15. Submit the PK/PD data from the comparison of 400 mg/day versus 800 mg/day in GIST patients in the two ongoing multicenter trials of imatinib (EORTC and NCI sponsored trials).

Prior commitment which is not a condition of accelerated approval of Gleevec for newly diagnosed CML patients (NDA 21-335/004 submitted June 28, 2002 and approved December 20, 2002):

18. To conduct a prospective study performed in patients receiving both Gleevec and a potent CYP3A4 inducer such as phenytoin, phenobarbital, or carbamazepine and submit a final study report. The purpose of this study is to determine the dose of Gleevec that is necessary to produce similar AUCs in these patients on enzyme inducers to those achieved in adult patients receiving the usual recommended dose (400 mg/day). Timeline: Protocol submission June 2003; study start date December 2003; and final report December 2004.

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 two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Dotti Pease, Regulatory Project Manager, at (301) 796-1434.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
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/

Robert Justice
10/19/2006 05:04:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

LABELING

NOVARTIS

T2006-XX

Gleevec®

(imatinib mesylate)

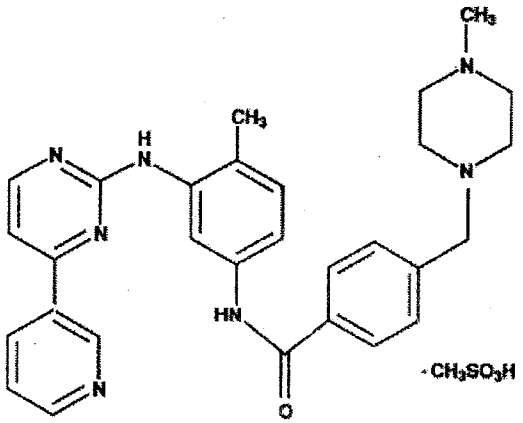
Tablets

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 $\leq$ 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-1,000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 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. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar to that of the parent compound.

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 hours 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: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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 = 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

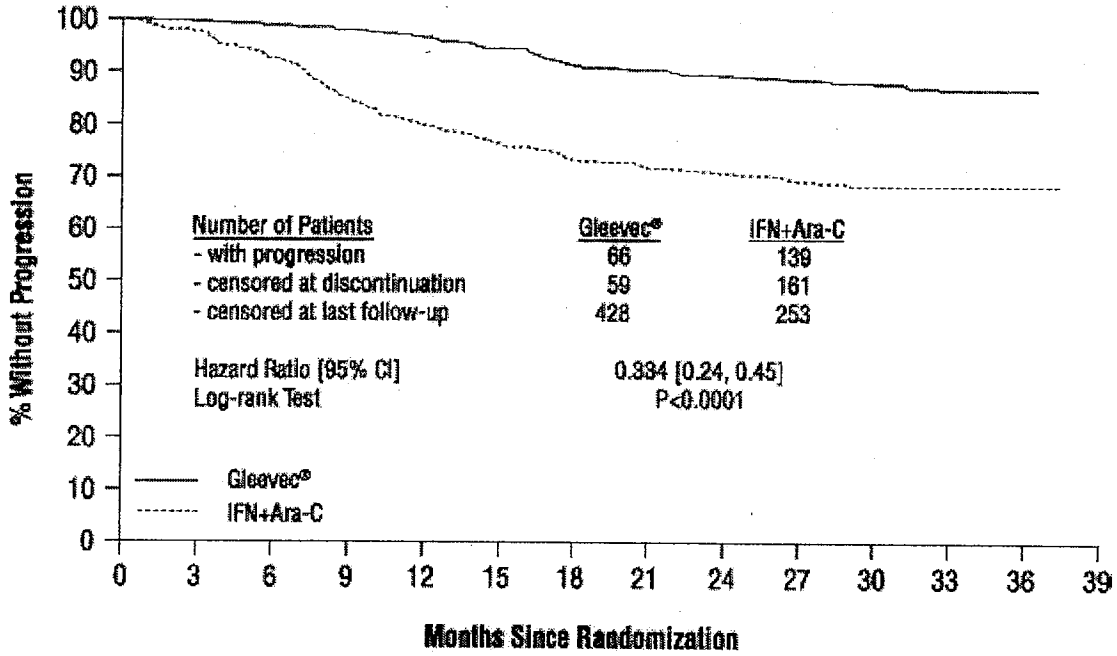
Chronic Phase, Newly Diagnosed: An open-label, multicenter, international randomized Phase 3 study has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent Gleevec® (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. Dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 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 1,106 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 ($p<0.0001$), (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 the 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

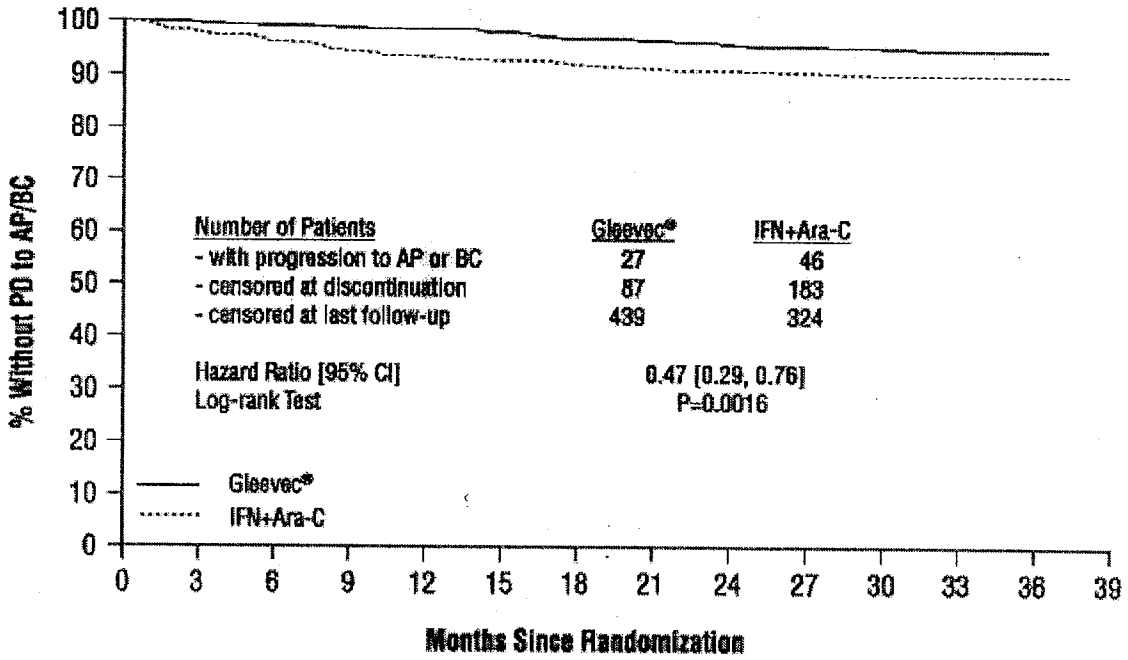
158 reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase
159 chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response
160 but without a major molecular response, and 82% in patients who were not in complete
161 cytogenetic response at this time point ($p<0.001$).
162

163 **Figure 1 Time to Progression (ITT)**



164
165

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



Major cytogenetic response, hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 2. Complete hematologic response, major cytogenetic response and complete cytogenetic response were also statistically significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

Table 2 Response in Newly Diagnosed CML Study (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 1,067 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-Alpha 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 3. 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 3. 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 3. 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 dose group (17% vs. 8%).

Table 3 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 1 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 maintained 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: A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients were treated with Gleevec 340 mg/m^2/day, with no interruptions in the absence of dose limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients after 8 weeks of therapy. The complete cytogenetic response rate (CCyR) was 65%,

comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months.

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in age from 3-20 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 a minimal cytogenetic response.

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

Acute Lymphoblastic Leukemia

A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Gleevec 600 mg/day in a phase 1 study.

Hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 4. The median duration of hematologic response was 3.4 months and the median duration of MCyR was 2.3 months.

Table 4: Effect of Gleevec on relapsed/refractory Ph+ ALL.

	Phase 2 Study (N=43)	Phase 1 Study (N=2)
CHR	8 (19%)	2 (100%)
NEL	5 (12%)	
RTC/PHR	11 (26%)	
MCyR	15 (35%)	
CCyR	9 (21%)	
PCyR	6 (14%)	

Myelodysplastic / Myeloproliferative diseases

An open label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These

patients were treated with Gleevec 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received Gleevec at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response). Sixteen patients had a translocation, involving chromosome 5q33 or 4p12, resulting in a PDGFR gene re-arrangement. All of these patients responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1(7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in table 5. Response durations of phase 2 study patients ranged from 141+ days to 457+ days.

Table 5 Response in MDS/MPD

	N	Complete hematological response	Major Cytogenetic response
		N (%)	N (%)
Overall population	31	14 (45)	12 (39)
Chromosome 5 translocation	14	11 (79)	11 (79)
Chromosome 4 translocation	2	2 (100)	1 (50)
Others / no translocation	14	1 (7)	0 (0)
Molecular relapse	1	NE	NE

NE: Not evaluable

Aggressive Systemic Mastocytosis

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic mastocytosis (ASM). The ASM patients were treated with 100 mg to 400 mg of Gleevec daily. These 5 patients ranged from 49 to 74 years of age. In addition to these 5 patients, 10 published case reports and case series describe the use of Gleevec in 23 additional patients with ASM aged 26 to 85 years. These 23 patients also received 100 mg to 400 mg of Gleevec daily.

Cytogenetic abnormalities were evaluated in 20 of the 28 ASM patients treated with Gleevec from the published reports and in the phase 2 study. Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML.

Of the total population of 28 patients treated for ASM, 8 (29%) achieved a complete hematologic response and 9 (32%) a partial hematologic response (61% overall response rate). Median duration of Gleevec therapy for the 5 ASM patients in the phase 2 study was 13 months (range 1.4-22.3 months) and between 1 month and more than 30 months in the responding patients described in the published medical literature. A summary of the response rates to Gleevec in ASM is provided in Table 6. Response durations of literature patients ranged from 1+ to 30+ months.

Table 6 Response in ASM

Cytogenetic abnormality	Number of patients	Complete hematologic response N (%)	Partial hematologic response N (%)
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	7	7(100%)	0
Juxtamembrane mutation	2	0 (0%)	2 (100%)
Unknown or no cytogenetic abnormality detected	15	0(0%)	7 (44%)
D816V mutation	4	1* (25%)	0
Total	28	8 (29%)	9 (32%)

*Patient had concomitant CML and ASM

Gleevec has not been shown to be effective in patients with less aggressive forms of systemic mastocytosis (SM). Gleevec is therefore not recommended for use in patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), SM with an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

Hypereosinophilic Syndrome / Chronic Eosinophilic Leukemia

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 14 patients with Hypereosinophilic

Syndrome/Chronic Eosinophilic Leukemia (HES/CEL). HES patients were treated with 100 mg to 1000 mg of Gleevec daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily. Hematologic response rates are summarized in Table 7. Response durations for literature patients ranged from 6+ weeks to 44 months.

Table 7 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematological response N (%)	Partial hematological response N (%)
Positive FIP1L1-PDGFRα fusion kinase	61	61 (100%)	0
Negative FIP1L1-PDGFRα fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	23 (13%)

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22. This translocation results in the fusion of 2 genes, the collagen type 1 alpha 1 gene and the PDGF B gene.

An open label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with Gleevec 800 mg daily. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial surgical resection and not considered amenable to further surgery at the time of study entry. A further 6 DFSP patients treated with Gleevec are reported in 5 published case reports, their ages ranging from 18 months to 49 years. The total population treated for DFSP therefore comprises 18 patients, 8 of them with metastatic disease. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Gleevec daily. A single pediatric patient received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily. Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. Responses to treatment are described in Table 8.

Table 8 Response in DFSP

	Number of patients (n=18)	%
Complete response	7	39
Partial response *	8	44
Total responders	15	83

* 5 patients made disease free by surgery

Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of them completely (37%). For the 10 study patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.

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 36 months. The study was not powered to show a statistically significant difference in response rates between the 2 dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit (CD117) 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 9.

Table 9 Tumor Response in GIST Trial

	(N=147) 400 mg n= 73 600 mg n=74 n (%)
Complete Response	1(0.7)
Partial Response	98 (66.7%)
Total (CR + PR)	99 (67.3% with 95% C.I. 59.1, 74.8)

There were no differences in response rates between the 2 dose groups. For the 99 responders to imatinib observed in the GIST study, the Kaplan-Meier estimate of median duration of response is 118 weeks (95% CI: 96, not reached) The median time to response was 12 weeks (range was 3-98 weeks).

INDICATIONS AND USAGE

Gleevec® (imatinib mesylate) is indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Follow-up is limited.
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ 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.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- 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. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

There have been post-marketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with Gleevec.

Gastrointestinal Disorders: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

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. In pediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy. (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).

Hepatic Impairment: Comparable exposure was noted between each of the mildly and moderately hepatically-impaired patients and patients with normal hepatic function. However, patients with severe hepatic impairment tended to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function (See CLINICAL PHARMACOLOGY and DOSING AND ADMINISTRATION). Patients with severe hepatic impairment should be closely monitored.

Hypereosinophilic cardiac Toxicity: In patients with hypereosinophilic syndrome and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Myelodysplastic/ myeloproliferative disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Severe congestive heart failure and left ventricular dysfunction: Severe congestive heart failure and left ventricular dysfunction have occasionally been reported in patients taking Gleevec. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The urogenital tract from a 2-year carcinogenicity study in rats receiving doses of 15, 30 and 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary bladder papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation of other organs in the rats is ongoing.

The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day (approximately 0.5 to 4 times the human daily exposure at 400 mg/day). The kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day. No tumors in the urogenital tract were observed at 15 mg/kg/day.

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/day, 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 in children with newly diagnosed Ph+ chronic phase CML and 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 2 years of age. Follow-up in children with newly diagnosed Ph+ chronic phase CML is limited.

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-alpha 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 10 for newly diagnosed CML, Table 11 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 1.1%-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 threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated in the Gleevec studies are shown in Tables 10 and 11.

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

	All Grades		CTC Grades 3/4	
	Gleevec®	IFN+Ara-C	Gleevec®	IFN+Ara-C
Preferred Term	N=551 (%)	N=533 (%)	N=551 (%)	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	61.5	0.9	5.1
Muscle Cramps	43.2	11.4	1.6	0.2
Musculoskeletal Pain	39.2	44.1	3.4	8.1
Diarrhea	38.5	42	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 Hemorrhage	1.3	1.1	0.5	0.2
- CNS Hemorrhage	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 Repiratory 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

673 (1) All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship
674 to treatment.

675 **Table 11 Adverse Experiences Reported in Other CML Clinical Trials (≥10% of all**
676 **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
- GI 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

677 (1) All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship
678 to treatment.

679 (2) Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial
680 effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

681 ## Hematologic Toxicity

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

685 In patients with newly diagnosed CML, cytopenias were less frequent than in the other
686 CML patients (see Tables 12 and 13). The frequency of grade 3 or 4 neutropenia and
687 thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase
688 compared to chronic phase (see Tables 12 and 13). The median duration of the neutropenic
689 and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks,
690 respectively.

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

694 ## Hepatotoxicity

695 Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 12) and were
696 usually managed with dose reduction or interruption (the median duration of these episodes
697 was approximately 1 week). Treatment was discontinued permanently because of liver
698 laboratory abnormalities in less than 0.5% of CML patients. However, one patient, who was
699 taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade
700 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and grade 3 or 4 SGOT
701 (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in
702 2.7% of patients.

703 ## Adverse Reactions in Pediatric Population

704 The overall safety profile of pediatric patients treated with Gleevec in 93 children studied was
705 similar to that found in studies with adult patients, except that musculoskeletal pain was less
706 frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most
707 commonly reported individual AEs with an incidence similar to that seen in adult patients.
708 Although most patients experienced AEs at some time during the study, the incidence of
709 Grade 3/4 AEs was low.

710 ## Adverse Effects in Other Subpopulations

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

716 **Table 12 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

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

718

719 **Table 13 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	4.6	0	5.5	0.4	0.2	0

Phosphatase						
– 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 10^9/L), 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)

Acute Lymphoblastic Leukemia

The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported drug-related adverse events reported in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

Myelodyplastic/Myeloproliferative Diseases

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec for MDS/MPD in the phase 2 study, are shown in Table 14.

Table 14 Adverse Experiences Reported (more than one patient) in MPD Patients in the phase 2 study (≥10% all patients) all Grades

Preferred term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)
Muscle cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital edema	2 (28.6)

Aggressive Systemic Mastocytosis

All ASM patients experienced at least one adverse event at some time. The most frequently reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritis, rash and lower respiratory tract infection. None of the 5 patients in the phase 2 study with ASM discontinued Gleevec due to drug-related adverse events or abnormal laboratory values.

Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile in the HES/CEL patient population does not appear to be different from the known safety profile of imatinib observed in other hematologic malignancy populations, such as CML. All patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC grade 3 leukopenia, neutropenia, lymphopenia and anemia.

Dermatofibrosarcoma Protuberans

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Gleevec for DFSP in the phase 2 study are shown in Table 15.

Table 15 Adverse Experiences Reported in DFSP Patients in the Phase 2 Study (≥10% all patients) all Grades

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital edema	4 (33.3)
Face edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye edema	4 (33.3)
Lacrimation increased	3 (25.0)
Dyspnea exertional	2 (16.7)
Anemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Gleevec for DFSP in the phase 2 study are presented in Table 16.

Table 16 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study

	N=12	
CTC Grades	**Grade 3**	**Grade 4**
Hematology Parameters		

- Anemia	17 %	0 %
- Thrombocytopenia	17 %	0 %
- Neutropenia	0 %	8 %
Biochemistry Parameters		
- Elevated Creatinine	0 %	8 %

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),

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 7 patients (5%) 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 17. 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 17 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)	
	400 mg (n=73)	600 mg (n=74)	400 mg (n=73)	600 mg (n=74)
Preferred Term	%	%	%	%
Fluid Retention	81	80	7	12
- Superficial Edema	81	77	6	5
- Pleural Effusion or Ascites	15	12	3	8
Diarrhea	59	70	3	7

Nausea	63	74	6	4
Fatigue	48	53	1	1
Muscle Cramps	47	58	0	0
Abdominal Pain	40	37	11	4
Rash and Related Terms	38	53	4	3
Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1
Headache	33	39	0	0
Flatulence	30	34	0	0
Any Hemorrhage	26	34	6	11
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	4	4	4	3
- Other Hemorrhage[2]	22	27	0	5
Pyrexia	25	16	3	0
Back Pain	23	26	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper Respiratory Tract Infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0
Loose Stools	12	10	0	0
Operation	12	8	6	4
Pharyngolaryngeal Pain	12	7	0	0
Joint Pain	11	15	1	0
Constipation	11	10	0	1
Anxiety	11	7	0	0
Taste Disturbance	3	15	0	0

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

[2] This category includes conjunctival hemorrhage, blood in stool, epistaxis, hematuria, post-procedural hemorrhage, bruising, and contusion.

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 18.

Table 18 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	8	1
– Thrombocytopenia	0	0	1	0
– Neutropenia	7	3	8	3
Biochemistry Parameters				
– Elevated Creatinine	0	0	3	0
– Reduced Albumin	3	0	4	0
– Elevated Bilirubin	1	0	1	3
– Elevated Alkaline Phosphatase	0	0	3	0
– Elevated SGOT (AST)	4	0	3	3
– Elevated SGPT (ALT)	6	0	7	1

CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 109/L, Grade 4 <0.5 x 109/L), thrombocytopenia (Grade 3 ≥10 - 50 x 109/L, Grade 4 <10 x 109/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, acute febrile neutrophilic dermatosis (Sweet's syndrome)

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

Rare: colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor necrosis, gastrointestinal perforation (see PRECAUTIONS)

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

Hematologic: *Infrequent*: pancytopenia

Rare: aplastic anemia

Hepatobiliary: *Uncommon*: hepatitis

rare: hepatic failure

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

Rare: avascular necrosis/hip osteonecrosis

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® (imatinib mesylate) 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 1,200 mg of Gleevec daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse events. 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. 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 hematological malignancies or malignant sarcomas, as appropriate.

Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)

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 dosage of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m^2/day (not to exceed 600 mg). 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.

Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)

The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

Myelodysplastic/Myeloproliferative diseases (MDS/MPD)

The recommended dosage of Gleevec is 400 mg/day for adult patients with MDS/MPD.

Aggressive systemic mastocytosis (ASM)

The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be

considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Hypereosinophilic syndrome/chronic eosiniphilic leukemia (HES/CEL)

For adult patients with HES/CEL the recommended dose of Gleevec is 400 mg/day. HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dermatofibrosarcoma protuberans (DFSP)

The recommended dose of Gleevec is 800 mg/day for adult patients with DFSP.

Gastrointestinal stromal tumors (GIST)

The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

General Information

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 2 years of age.

Patients with mild and moderate hepatic impairment should be treated at a starting dose of 400 mg/day. Patients with severe hepatic impairment should be treated at a starting dose of 300 mg/day. (See CLINICAL PHARMACOLOGY and PRECAUTIONS)

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.

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.

For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron.

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, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m^2/day to 260 mg/m^2/day or from 260 mg/m^2/day to 200 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 19.

Table 19 Dose Adjustments for Neutropenia and Thrombocytopenia

ASM associated with eosinophilia (starting dose 100 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Gleevec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction).
HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1.0 x 10^9/L and/or platelets < 50 x10^9/L	1. Stop Gleevec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction).
Chronic Phase CML (starting dose 400 mg) MDS/MPD, ASM and HES/CEL (starting dose 400 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 or 600 mg 3. If recurrence of ANC <1.0 x 10^9/L

GIST (starting dose either 400 mg or 600 mg)		and/or platelets <50 x 10^9/L, repeat step 1 and resume Gleevec at a reduced dose (300 mg if starting dose was 400 mg, 400 mg if starting dose was 600 mg)
Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg) Ph+ ALL (starting dose 600 mg)	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 persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 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
DFSP (starting dose 800 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Gleevec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Gleevec at 600 mg 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Gleevec at reduced dose of 400 mg.
Newly diagnosed pediatric chronic phase CML (start at dose 340 mg/m^2)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Gleevec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Gleevec at reduced dose of 260 mg/m^2
Pediatric patients with chronic phase CML recurring after transplant or resistant to Interferon (start at dose 260 mg/m2	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Gleevec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Gleevec at previous dose (i.e. before severe adverse reaction) 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Gleevec at reduced dose of 200 mg/m^2

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 "400" on one side with score on the other side, and "SL" on each side of the score.

Bottles of 30 tablets.....NDC 0078-0438-15

Storage

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

Dispense in a tight container, USP.

T2006-XX-XX

REV: 2006 XXXXXXX 2006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

SUMMARY REVIEW

Division Director Summary Review of an Efficacy Supplement

NDA: 21-588/S-011
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 17, 2006

This efficacy supplement seeks approval of Gleevec for the treatment of "Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)." The following summary of safety and effectiveness data is taken from the draft labeling.

Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22. This translocation results in the fusion of 2 genes, the collagen type 1 alpha 1 gene and the PDGF B gene.

An open label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with Gleevec 800 mg daily. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial surgical resection and not considered amenable to further surgery at the time of study entry. A further 6 DFSP patients treated with Gleevec are reported in 5 published case reports, their ages ranging from 18 months to 49 years. The total population treated for DFSP therefore comprises 18 patients, 8 of them with metastatic disease. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Gleevec daily. A single pediatric patient received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily. Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. Responses to treatment are described in Table 8.

Table 8 Response in DFSP

	Number of patients (n=18)	%
Complete response	7	39
Partial response *	8	44
Total responders	15	83

* 5 patients made disease free by surgery

Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with

metastatic disease, five responded (62%), three of them completely (37%). For the 10 study patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Gleevec for DFSP in the phase 2 study are shown in Table 15.

Table 15 Adverse Experiences Reported in DFSP Patients in the Phase 2 Study (≥10% all patients) all Grades

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital edema	4 (33.3)
Face edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye edema	4 (33.3)
Lacrimation increased	3 (25.0)
Dyspnea exertional	2 (16.7)
Anemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Gleevec for DFSP in the phase 2 study are presented in Table 16.

Table 16 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study

	N=12	
CTC Grades	**Grade 3**	**Grade 4**
Hematology Parameters		
- Anemia	17 %	0 %
- Thrombocytopenia	17 %	0 %
- Neutropenia	0 %	8 %
Biochemistry Parameters		
- Elevated Creatinine	0 %	8 %

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),

Clinical and Statistical Review

A combined Clinical and Statistical Review by Martin Cohen, M.D. and Kun He, Ph.D. was completed on September 9, 2006. The review made the following recommendation on regulatory action.

> The reviewing medical officer recommends regular approval of the proposed indication: "Gleevec is indicated for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)". Clinical benefit is demonstrated by a complete response rate of 39% and by the fact that partial responses allowed patients to be rendered disease free by surgery. DFSP has a characteristic t(17:22)(q22:q13) translocation involving platelet-derived growth factor B-chain (PDGFß) genes that makes DFSP a logical candidate for Gleevec treatment. This translocation was identified in 10 out of the 18 study patients comprising this report (10 out of 13 with available cytogenetics). The 3 patients without the translocation had complex cytogenetic abnormalities. One of the three had a treatment response. The rarity of occurrence of DFSP makes randomized trials impractical.

Clinical Inspection Summary

The Clinical Inspection Summary by Lloyd Johnson, Pharm.D. is dated July 3, 2006. Two clinical investigators and sites from study B2225 were inspected: Dr. George Demetri of the Dana-Farber Cancer Institute and Dr. Richard Silver of the New York Hospital-Cornell. The inspection summary's overall assessment of findings is quoted below.

> In general, for the two study sites inspected, it appears that sufficient documentation to assure that study subjects audited at the two sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D., was completed on September 21, 2006. Dr. Bullock recommended the following.

The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on February 28, 2006 and recommended approval from the standpoint of CMC.

Conclusion

I concur with the reviewers' recommendations that the supplement should be approved. Although the dataset is limited, this is a rare disease in which Gleevec has demonstrated clinically meaningful activity with acceptable toxicity.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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Robert Justice
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MEDICAL OFFICER

Division Director Summary Review of an Efficacy Supplement

NDA: 21-588/S-012
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 17, 2006

This efficacy supplement seeks approval of Gleevec for the treatment of "Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements." The following summary of safety and effectiveness data is taken from the draft labeling.

An open label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These patients were treated with Gleevec 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received Gleevec at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response). Sixteen patients had a translocation involving chromosome 5q33 or 4p12, resulting in a PDGFR gene re-arrangement. All of these responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in table 5. Response durations of phase 2 study patients ranged from 141+ days to 457+ days.

Table 5 Response in MDS/MPD

	N	Complete hematological response	Major Cytogenetic response
		N (%)	N (%)
Overall population	31	14 (45)	12 (39)
Chromosome 5 translocation	14	11 (79)	11 (79)
Chromosome 4 translocation	2	2 (100)	1 (50)
Others / no translocation	14	1 (7)	0 (0)
Molecular relapse	1	NE	NE

NE: Not evaluable

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec for MDS/MPD in the phase 2 study, are shown in Table 14.

Table 14 Adverse Experiences Reported (more than one patient) in MPD Patients in the phase 2 study (≥10% all patients) all Grades

Preferred term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)
Muscle cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital edema	2 (28.6)

Clinical and Statistical Review

A combined Clinical and Statistical Review by Martin Cohen, M.D. and Kun He, Ph.D. was completed on September 13, 2006. The review made the following recommendation on regulatory action.

The medical reviewer recommends that regular approval be granted for the proposed indication "Gleevec is indicated for the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements". Clinical benefit is demonstrated by long duration responses. Further, the rarity of occurrence of myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements makes randomized trials impractical. To prevent confusion with standard MDS this entity is best called MPD/MDS.

Clinical Inspection Summary

Clinical inspections were not requested for this supplement.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D., was completed on September 21, 2006. Dr. Bullock recommended the following:

The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on February 28, 2006 and recommended approval from the standpoint of CMC.

Conclusion

I concur with the reviewers' recommendations that the supplement should be approved. Although the dataset is limited, this is a rare disease in which Gleevec has demonstrated clinically meaningful efficacy with acceptable toxicity.

Robert L. Justice, M.D., M.S.

Director

Division of Drug Oncology Products

Office of Oncology Drug Products

Office of New Drugs

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Robert Justice
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Division Director Summary Review of an Efficacy Supplement

NDA: 21-588/S-013
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 17, 2006

This efficacy supplement seeks approval of Gleevec for the treatment of "Adult patients with relapsed or refractory Ph+ ALL." The following summary of safety and effectiveness data is taken from the draft labeling.

A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Gleevec dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Gleevec 600 mg/day in a phase 1 study.

Hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 4. The median duration of hematologic response was 3.4 months and the median duration of MCyR was 2.3 months.

Table 4: Effect of Gleevec on relapsed/refractory Ph+ ALL

	Phase 2 Study (N=43)	Phase 1 Study (N=2)
CHR	8 (19%)	2 (100%)
NEL	5 (12%)	
RTC/PHR	11 (26%)	
MCyR	15 (35%)	
CCyR	9 (21%)	
PCyR	6 (14%)	

The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported drug-related adverse events reported in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

Clinical and Statistical Review

A combined Clinical and Statistical Review by Martin Cohen, M.D. and Kun He, Ph.D. was completed on September 8, 2006. The review made the following recommendation on regulatory action.

> The clinical reviewer recommends that Gleevec receive regular approval for the treatment of adult patients with relapsed/refractory Ph+ ALL. This is based upon the induction of both hematologic and cytogenetic responses in this patient population. For the 7 Ph+ ALL/LBC patients in the phase 1 study (03001) who received Gleevec doses of 600 mg/day or higher 3 had a complete hematologic response (CHR). For the 43 patients with Ph+ ALL treated with Gleevec 600 mg/day in the phase 2 study (0109) there were 3 confirmed CHR's (7%), 0 NEL (no evident leukemia) and 7 RTC/PR's (16%) in the sponsor analysis. In the sponsor analysis of unconfirmed hematologic responses there were 8 CHR's (19%), 3 NEL's (7%) and 13 RTC/PR's (30%). In the FDA analysis that included both confirmed and unconfirmed responses there were 8 CHR's (19%), 5 NEL's (12%) and 11 RTC's (26%).
>
> Major cytogenetic responses (complete or partial; confirmed or unconfirmed) were seen in 15 (35%) of 43 Ph+ ALL phase 2 patients who received Gleevec 600 mg/day. Of the 15 patients with MCyR, 9 (21%) achieved CCyR (6 confirmed) and 6 (14%) had a PCyR (3 confirmed).
>
> The median time to progression in study 0109 was 2.6 months (95% CI 1.9, 3.0). In the expanded access study 0114 the median TTP was 3.1 months (95% CI 3.0, 4.0).
>
> Gleevec was generally well tolerated. The most frequently reported non-hematological AEs included nausea, vomiting, pyrexia and peripheral edema. In the population of older patients (= 55 years) the efficacy and safety results were comparable to those obtained in the younger population (< 55 years old). No new safety concerns were raised.

Clinical Inspection Summary

The Clinical Inspection Summary by Lloyd Johnson, Pharm.D. is dated July 3, 2006. Two clinical investigators and sites from study B2225 were inspected: Dr. George Demetri of the Dana-Farber Cancer Institute and Dr. Richard Silver of the New York

Hospital-Cornell. The inspection summary's overall assessment of findings is quoted below.

> In general, for the two study sites inspected, it appears that sufficient documentation to assure that study subjects audited at the two sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D., was completed on September 21, 2006. Dr. Bullock recommended the following.

> The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on March 22, 2006 and recommended approval from the standpoint of CMC.

Conclusion

I concur with the reviewers' recommendations that this supplement should be approved. Although the dataset is limited, this is an uncommon disease in which Gleevec induced complete hematologic responses in 19% of patients and no evidence of leukemia in 12%. In addition 35% of patients had major cytogenetic responses. Although the response durations were brief, the toxicity was acceptable and this patient population needs additional therapeutic alternatives.

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Robert Justice
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Division Director Summary Review of an Efficacy Supplement

NDA: 21-588/S-014
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 17, 2006

This efficacy supplement seeks approval of Gleevec for the treatment of "Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown." The following summary of safety and effectiveness data is taken from the draft labeling.

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic mastocytosis (ASM). The ASM patients were treated with 100 mg to 400 mg of Gleevec daily. These 5 patients ranged from 49 to 74 years of age. In addition to these 5 patients, 10 published case reports and case series describe the use of Gleevec in 23 additional patients with ASM aged 26 to 85 years. These 23 patients also received 100 mg to 400 mg of Gleevec daily.

Cytogenetic abnormalities were evaluated in 20 of the 28 ASM patients treated with Gleevec from the published reports and in the phase 2 study. Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to Gleevec), one with concomitant CML.

Of the total population of 28 patients treated for ASM, 8 (——) achieved a complete hematologic response and 9 (32%) a partial hematologic response (—— overall response rate). Median duration of Gleevec therapy for the 5 ASM patients in the phase 2 study was 13 months (range 1.4-22.3 months) and between 1 month and more than 30 months in the responding patients described in the published medical literature. A summary of the response rates to Gleevec in ASM is provided in Table 6. Response durations of literature patients ranged from 1+ to 30+ months.

b(4)

Table 6 Response in ASM

Cytogenetic abnormality	Number of patients	Complete hematologic response N (%)	Partial hematologic response N (%)
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	7	7(100%)	0
Juxtamembrane mutation	2	0 (0%)	2 (100%)
Unknown or no cytogenetic abnormality detected	15	0(0%)	7 (44%)
D816V mutation	4	1* (25%)	0
Total	28	8 (—)	9 (32%)

*Patient had concomitant CML and ASM

b(4)

Gleevec has not been shown to be effective in patients with less aggressive forms of systemic mastocytosis. Gleevec is therefore not recommended for use in patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

All ASM patients experienced at least one adverse event at some time. The most frequently reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritis, rash and lower respiratory tract infection. None of the 5 patients in the phase 2 study with ASM discontinued Gleevec due to drug-related adverse events or abnormal laboratory values.

Clinical and Statistical Review

A combined Clinical and Statistical Review by Martin Cohen, M.D. and Kun He, Ph.D. was completed on September 13, 2006. The review made the following recommendation on regulatory action.

The medical reviewer recommends that regular approval be granted for the following indication:. "Gleevec is indicated for the treatment adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown". Approval does not include patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological

non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

Clinical benefit is demonstrated by long duration responses. Further, the rarity of occurrence of aggressive SM with absent c-Kit D816V mutation makes randomized trials impractical. The number of patients suffering from smoldering and aggressive SM in the USA is estimated to be 20,000, among which 8,000 are adults and 12,000 children. Kit D816V mutation is present in approximately 60% of the adults, leaving 3000 adults without D816V mutation. Aggressive mastocytosis represents less than 5% of adult cases or less than 150 patients.

A summary of responses in aggressive SM is shown below.

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	7	7 (100%)	0
Juxtamembrane mutation	2	0	2 (100%)
Unknown or no cytogenetic abnormality detected	15	0	7 (44%)
D816V mutation	4	1* (25%)	0
Total	28	8 (30%)	9 (32%)

*Patient had concomitant CML and SM

The review had the following phase 4 request.

Assure availability of a validated test kit for detection of the D816V c-kit mutation. An IDE or Pre-Market Application filing by Novartis or a 3rd party should occur no later than 4 months after Gleevec approval for this indication.

Clinical Inspection Summary

Clinical inspections were not requested for this supplement.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D., was completed on September 21, 2006. Dr. Bullock recommended the following.

> The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on May 22, 2006 and recommended approval from the standpoint of CMC.

Conclusion

I concur with the reviewers' recommendations that the supplement should be approved. Although the dataset is limited, this is a rare disease in which Gleevec has demonstrated clinically meaningful efficacy with acceptable toxicity.

Robert L. Justice, M.D., M.S.
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Robert Justice
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MEDICAL OFFICER

Addendum to Division Director Summary Review

NDA: 21-588/S-017
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 18, 2006

The applicant noted an error in Table 7 of the draft label which was quoted in my review. There were 9, rather than 16, partial responders who were negative for the FIP1L1-PDGFRα fusion kinase. This was confirmed by the medical reviewer, Dr. Martin Cohen. The correct response rates are show below.

Table 7 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematological response N (%)	Partial hematological response N (%)
Positive FIP1L1-PDGFRα fusion kinase	61	61 (100%)	0
Negative FIP1L1-PDGFRα fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	[redacted]

b(4)

This correction does not change my recommendation for approval of the supplement.

Robert L. Justice, M.D.
Division Director
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Office of Oncology Drug Products
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Division Director Summary Review of an Efficacy Supplement

NDA: 21-588/S-017
Drug: Gleevec (imatinib mesylate) Tablets
Applicant: Novartis Pharmaceuticals Corporation
Date: October 17, 2006

This efficacy supplement seeks approval of Gleevec for the treatment of "Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who demonstrate either the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) as well as for patients who are FIP1L1-PDGFRα fusion kinase negative or unknown."

The following summary of safety and effectiveness data is taken from the draft labeling.

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 14 patients with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia (HES/CEL) HES patients were treated with 100 mg to 1000 mg of Gleevec daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily. Hematologic response rates are summarized in Table 7. Response durations for literature patients ranged from 6+ weeks to 44 months.

Table 7 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematological response N (%)	Partial hematological response N (%)
Positive FIP1L1-PDGFRα fusion kinase	61	61 (100%)	0
Negative FIP1L1-PDGFRα fusion kinase	56	12 (21%)	[redacted]
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	23 (13%)

b(4)

The safety profile in the HES/CEL patient population does not appear to be different from the known safety profile of imatinib observed in other hematologic malignancy populations, such as CML. All patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC grade 3 leukopenia, neutropenia, lymphopenia and anemia.

Clinical and Statistical Review

A combined Clinical and Statistical Review by Martin Cohen, M.D. and Kun He, Ph.D. was completed on September 13, 2006. The review made the following recommendation on regulatory action.

> The medical reviewer recommends that regular approval be granted. Clinical benefit is demonstrated by long duration responses. The overall CHR rate was 61% and the PHR rate was 9%. Response durations for the 4 HES PR's in study B2225 were at least 348, 394, 131 and 183 days and response durations in literature patients ranged from 1.5+ months to 44 months. In addition, the rarity of occurrence of HES with or without demonstrated FIP1L1-PDGFRa fusion kinase makes randomized trials impractical.
>
> Availability of an assay for the FIP1L1-PDGFRa fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) is necessary because the Gleevec starting dose for such patients is 100 mg/day.

The review also recommended the following phase 4 request.

> Assure availability of a validated test kit for detection of the FIP1L1-PDGFRa fusion kinase, as determined either directly by mutational analysis or by demonstration of a CHIC2 allele deletion by FISH methodology that implies the presence of the FIP1L1- PDGFRa fusion kinase. The Pre-Market Application (PMA) filing by a 3rd party should occur 3 months after approval.

Clinical Inspection Summary

Clinical inspections were not requested for this supplement.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Julie Bullock, Pharm.D., was completed on September 21, 2006. Dr. Bullock recommended the following.

The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on June 28, 2006 and recommended approval from the standpoint of CMC.

Conclusion

I concur with the reviewers' recommendations that the supplement should be approved. Although the dataset is limited, this is a rare disease in which Gleevec has demonstrated durable complete hematologic responses with acceptable toxicity. The proposed test kit for detection of the FIP1L1-PDGFRa fusion kinase will identify patients who are more likely to benefit from the drug.

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/s/

Robert Justice
10/17/2006 06:23:27 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

MEDICAL REVIEW(S)
STATISTICAL REVIEW(S)

Application Type	NDA 21-588
Submission Number	SE1
Submission Code	012 (MDS/MPD)
Letter Date	12/19/05
Stamp Date	12/19/05
Reviewer Name	Martin H. Cohen, M.D.
Statistician	Kun He, Ph.D.
Review Completion Date	6/01/06
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	S

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 with myelodysplastic syndrome/myeloproliferative disease (MDS/MPD).

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(s)

Proposed Indication: Gleevec is indicated for the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements

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. MDS/MPD patients may have a chromosome 5 translocation presumably involving PDGFRβ or a chromosome 4 translocation presumably involving PDGFRα.

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1.0 EXECUTIVE SUMMARY

The purpose of the present submission is to present data to support the proposed indication:

The current submission includes efficacy and safety data for 7 patients with MDS/MPD treated in an open label, multicenter, Phase II clinical trial (study B2225) and a further 24 patients with MDS/MPD who were summarized in 13 published studies. Of the total 31 patients, 4 study B2225 patients and 10 literature patients had a chromosome 5 translocation presumably involving PDGFRβ and 2 literature patients had a chromosome 4 translocation presumably involving PDGFRα. Of the 4 B2225 patients with a chromosome 5 translocation imatinib treatment produced complete hematologic and cytogenetic responses in 2 patients and a long duration partial response in a third patient. The fourth patient was non-evaluable. One additional B2225 complete responder had a non-evaluable karyotype. Of the 10 literature patients with a chromosome 5 translocation 9 had complete haematological responses of 4+ months to 18+ months duration (median 11+ months). Eight of these patients also had a complete cytogenetic response and the remaining patient had a major cytogenetic resoponse. Of the 2 literature patients with a chromosome 4 translocation both had complete hematologic responses of 3+ months and 7+ months duration with imatinib treatment..

1.2 Recommendation On Regulatory Action

The medical reviewer recommends that regular approval be granted for the proposed indication "Gleevec is indicated for the treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements". Clinical benefit is demonstrated by long duration responses. Further, the rarity of occurrence of myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements makes randomized trials impractical. To prevent confusion with standard MDS this entity is best called MPD/MDS.

1.3 Recommendation On Post-marketing Actions

Continue post-marketing surveillance.

1.3.1 Risk Management Activity

Continue post-marketing surveillance of AE's

1.3.2 Required Phase 4 Commitments

None

1.3.3 Other Phase 4 Requests

Assure availability of a validated test kit for detection of PDGFR gene rearrangement by FISH analysis. The Pre-Market Application (PMA) filing by a 3rd party should occur by 4 months after approval.

1.4 SUMMARY OF CLINICAL FINDINGS

1.4.1 Brief Overview of Clinical Program

The clinical program includes efficacy and safety data for 7 patients with MDS/MPD treated in an open label, multicenter, Phase II clinical trial (study B2225) and a further 24 patients with MDS/MPD who were summarized in 13 published reports.

1.4.2 Efficacy

Of the 7 MDS/MPD patients treated in study B2225 and the 24 patients with MDS/MPD summarized in the published literature 4 study B2225 patients and 10 literature patients had a chromosome 5 translocation presumably involving PDGFRβ and 2 literature patients had a chromosome 4 translocation presumably involving PDGFRα. Of the 4 B2225 patients with a chromosome 5 translocation imatinib treatment produced complete hematologic and cytogenetic responses in 2 patients and a long duration partial response in a third patient. The fourth patient was non-evaluable for response. One additional B2225 complete responder had a non-evaluable karyotype. Of the 10 literature patients with a chromosome 5 translocation 9 had complete haematological responses of 4+ months to 18+ months duration (median 11+ months). Eight of these patients also had a complete cytogenetic response and the remaining patient had a major cytogenetic response. Of the 2 literature patients with a chromosome 4 translocation both had complete hematologic responses of 3+ months and 7+ months duration with imatinib treatment. Of the 2 imatinib treated B2225 patients who had a normal karyotype and the 12 literature patients without a chromosome 5 translocation there was only 1 partial hematologic response.

1.4.3 Safety

Adverse events in MDS/MPD patients were similar to those observed in other Gleevec studies. Most were of CTC grade 1 or 2 in severity. AE's included nausea, diarrhea, fatigue, muscle cramps, arthralgia and fluid retention. Laboratory abnormalities included anemia.

MDS/MPD diseases might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should be therefore considered in patients with MDS/MPD diseases associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should therefore be considered at the initiation of therapy.

Follow-up, to-date indicate that the following toxicities may be of concern:

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome. In some reported cases a recurrent dermatologic reaction was observed upon rechallenge. Several 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. 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. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST. There have been post-marketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with Gleevec.

Gastrointestinal Disorders: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

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. 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.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Gleevec.

Toxicities From Long-Term Use: Potential toxicities suggested by animal studies, include 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).

1.4.4 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients with MDS/MPD.

1.4.5 Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: 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.

CYP3A4 Substrates: 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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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.

1.4.6 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.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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.

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 Abl tyrosine kinase at the in vitro, cellular, and in vivo level. The compound specifically inhibited proliferation of v-Abl and Bcr-Abl expressing cells, suggesting that it is not a general antimitotic agent. In colony formation assays using progenitor cells ex vivo from patients with CML, imatinib showed selective inhibition of Bcr-Abl positive colonies. In addition, imatinib potently inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ), c-Kit, the receptor for stem cell factor (SCF), c-Fms, the receptor for macrophage stimulating factor (M-CSF), as well as Abl and Arg PTK. Imatinib also inhibits the cell signaling events mediated by activation of Bcr-Abl, c-Kit and the PDGF receptors. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor, insulin and phorbol esters. In vivo, the compound shows anti-tumor activity as a single agent in animal models at well tolerated doses.

2.2 Currently Available Treatment For Proposed Indication

No treatment is approved for adult patients with MDS/MPD associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements. Drugs and procedures used for this condition include hydroxyurea, corticosteroids, interferon-alpha, Ara-C, etoposide, cyclosporine, busulfan, mercaptopurine, and bone marrow transplantation.

2.3 Availability Of Proposed Active Ingredient In The United States

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

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

The clinical results were discussed with the FDA on 12-Aug-2004. The objective of this meeting was to seek guidance for the approval of imatinib as a treatment for patients with rare malignancies carrying imatinib-sensitive targets. The FDA recognized the rarity of the targeted malignancies and accepted to consider a potential filing based upon an exploratory phase II study and published case reports/studies. Suggestions and recommendations on how to analyze and present the data were also given.

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_011\2005-12-16\

4.2 Table of Clinical Studies

Published clinical studies are summarized in **Table 2.** In addition, a phase II open label study [B2225] included 7 MDS/MPD patients.

Table 2: Published Clinical Studies

Study	No. of patients	Reference
MDS/MPD		
Wilkinson, et al (2003)	1	Blood 102:4187
Vizmanos, et al (2004)	1	Cancer Res 64:2673
Pardanani, et al (2003)	2	Blood 101:3391
Grand, et al (2004)	1	Cancer Res 64:7216
Levine, et al (2005)	1	Leukemia 19:27
Apperley, et al (2002)*	2	N Engl J Med 347:481
Total	8	
CMML		
Magnusson, et al (2002)	1	Blood 100:1088
Pitini, et al (2003a)	1	Haematologica 88:ECR18
Cortes, et al (2003)	3	Cancer 97: 2760
Total	5	
aCML		
Wittman, et al (2004)	1	Leukemia Res 28:S65
Garcia, et al (2003)	1	Blood 102:2699
Cortes, et al (2003)	7	Cancer 97:2760
Trempat, et al (2003)	1	Oncogene 22:5702
Safley, et al (2004)	1	Genes, Chromosomes and Cancer 40:44
Total	11	

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

DSI inspections are planned.

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice. The phase II clinical study was monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

4.6 Financial Disclosures

No clinical investigators in study 2225 are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are

identified on the spreadsheets by bolding the investigators name and are detailed in the disclosure forms that follow [FDA Form 3455]. These arrangements and interests were as follows (**Table 3**):

Table 3: Financial Disclosure Information

Investigator	Center No.	Amount Disclosed	Category of Disclosure
		>$25,000	
		>$25,000	
		$145,000	

b(6)

Financial disclosure information regarding the publications supporting this NDA submission was determined directly from the publication disclosure statements. The Authors either did not describe financial interest in any of the publications or stated that they had no conflict of interest or financial interest.

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 is indicated for the treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements

Myelodysplastic/myeloproliferative diseases while presenting with clinical characteristics of CML, are distinguished from the classic CML by the absence of the Philadelphia chromosome and the Bcr-Abl fusion oncoprotein. Three major disorders have been identified as part of this group of diseases: chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML) and juvenile myelomonocytic leukemia (JMML).

The molecular events that give rise to MDS/MPDs are poorly understood, but reciprocal chromosomal translocations that disrupt genes encoding receptor tyrosine kinases,

notably PDGFRβ at 5q31-35, PDGFRα 4q12, and FGFR1 at 8p11, have been found in some patients. As a consequence of these translocations, constitutively active fusion tyrosine kinases that are functionally and structurally analogous to Bcr-Abl are produced. Ritchie, et al (1999) investigated the role of a Tel-PDGFRβ fusion protein in the pathogenesis of the myeloproliferative subtype CMML. They found that mice which expressed the transgene that expresses Tel-PDGFRβ fusion protein exhibited dysregulated myelopoiesis with progression to myeloid or lymphoid malignancy. The investigators concluded that this murine model of CMML parallels a myeloproliferative syndrome in humans and implicates the Tel-PDGFRβ fusion protein in its pathogenesis. Although it is uncertain what proportion of MDS/MPDs actually involves PDGFR-related gene translocations, it is clearly an extremely rare diagnosis, with only a small number of case reports published to date. Because of the few case reports available, it is difficult to characterize the course of disease for patients with MDS/MPDs associated with PDGFR gene re-arrangements. It does seem appropriate to characterize them as myeloproliferative disorders Even though there is marked heterogeneity in clinical features, these patients present with a CML-like disease, usually with prominent eosinophilia, monocytosis, and splenomegaly. There appears to be a male bias in affected patients. Skin involvement may occur either as a consequence of aberrant PDGFR signaling, since this receptor is normally involved in wound healing and repair of skin lesions, or because of eosinophilic infiltrations. Patients have a complex clinical course involving thrombocytosis, thrombotic and hemorrhagic phenomena, constitutional symptoms, infections, and the potential for progression to myelofibrosis or acute leukemia. The latter appears to be relatively infrequent; in one large series of 34 patients only 15% transformed to an acute leukemia (Steer and Cross 2002).

Currently there are no known curative therapies for patients with these diseases. With increasing insight into the molecular pathogenesis of MDS/MPD associated with PDGFR gene re-arrangement, signal transduction-inhibitor therapy targeted to specific protein tyrosine kinases has been recognized as an important potential therapy for these conditions. The present application seeks approval of imatinib for the treatment of patients with MDS/MPD with PDGF gene re-arrangement on the basis of the data collected up to 31-Dec- 2004 in Study B2225 and of other published information up to 14-Oct-2005.

6.1.1 Methods

Clinical information concerning trial B2225 and the 13 referenced case reports were reviewed.

6.1.2 General Discussion of Endpoints

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

6.1.3 Study Design

Study B2225 is an open label, multicenter, phase II clinical trial testing the efficacy and safety of imatinib in patients suffering from life threatening diseases associated with Abl, Kit or PDGFR TKs. Patients had disease that was refractory to standard therapeutic options or for which no conventional therapies of definitive benefit existed. Tissue samples were to be collected and analyzed when possible and provided results to support the possible functional significance of one or more of the relevant imatinib-sensitive TKs. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, adequate end organ function, life expectancy of more than 3 months, adequate contraception and written, informed consent. Although patients were to have had a fresh tissue biopsy prior to study treatment and an additional biopsy while undergoing treatment, this was inconsistently done. Patients with hematologic malignancies (e.g. AML/myelodysplasia who displayed cytopenia) were eligible for the study despite thrombocytopenia and low absolute neutrophil count (ANC) if approved by Novartis after discussion with the investigator. Excluded from the study were patients eligible for other imatinib clinical protocols, treated with any other investigational agents within 28 days of first day of study drug dosing, had another primary malignancy or having received chemotherapy within 4 weeks (6 weeks for nitrosourea, mitomycin-C or any antibody therapy) prior to study entry. Patients were enrolled in the study over a 47-month period from 5-Feb-2001.

The planned starting dose differed between the two groups of malignancies, with the 45 patients with hematological malignancies initially receiving imatinib at 400 mg p.o. daily with a provision for a dose increase up to 800 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 4 weeks of therapy. The other 140 patients with solid tumors initially received imatinib at 800 mg p.o. daily with a provision for a dose increase up to 1000 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 8 weeks in solid tumor of therapy. Provisions for dose modification were included in the study protocol. Treatment was originally to be continued for 2 years; the protocol was later amended to allow indefinite treatment for patients benefiting from treatment in absence of safety concerns.

The primary objective of the study was to assess the efficacy of imatinib. The B2225 clinical study protocol as well as the published studies did not specifically distinguish between hematological and cytogenetic response as primary or secondary efficacy end-point, but hematological response was always used as primary endpoint, at least based upon the temporal evolution of events. Of note, no definition of response was included in the protocol for hematologic malignancies; the activity of imatinib was assessed primarily by evaluating normalization of blood counts and of bone marrow appearance, as well as cytogenetic analysis, FISH analysis for detection of PDGFR rearrangement and PCR analysis for its characterization.

Because these criteria used to asses the peripheral blood and the bone marrow response correspond to the definition of complete hematological and complete cytogenetic response used in other hematological malignancies, they are felt adequate to define the

therapeutic efficacy of the drug in the disease, and were used in all the case reports published and included in this application.

The defined secondary endpoint in was the ECOG status. No secondary endpoint was specified in the published case reports, although cytogenetic response could be also considered as a secondary endpoint.

Other secondary objectives were to assess the safety and tolerability of imatinib, to evaluate the pharmacokinetic (PK) profile of imatinib in selected patients and to assess, if feasible, the functional significance of relevant signal-transduction components in target tissues by evaluating the expression and activation status of the relevant tyrosine kinase molecules or associated signaling molecules, by measuring indices of cellular proliferation and by correlating the changes in the above findings with clinical outcomes. However, due to the inconsistent collection of biological samples, these latter secondary objectives were not evaluated.

Five to ten patients per indication, condition, or disease were initially enrolled. Lack of clinical efficacy excluded future patients with the same indication, condition or disease from the study. If however, evaluation of the results of the first five patients suggested a positive effect of imatinib by conventional clinical response criteria or other pharmacodynamic measures (e.g. decrease in 18-fluorodeoxyglucose (18-FDG) uptake by positron emission tomography (PET) scanning), additional patients with the same disease could have been enrolled into the study in order to enable adequate evaluation of imatinib effects.

6.1.3 Efficacy Findings

Study B2225 investigators are listed in **Table 4.**

Table 4: B2225 Investigators

Center	Principal Investigator	Study Facility	City, State	Country
101	Prof. Allan Van Oosterom	UZ Gasthuisberg dienst oncologie	Leuven	Belgium
201	Prof. Jane Apperley Prof. John Goldman	Hammersmith Hospitals Dept. of Hematology	London	United Kingdom
301	Dr. Luca Gianni	Istituto Nazionale Tumori	Milano	Italy
401	Dr. Jaap Verweij	Rotterdam Cancer Institute	Rotterdam	Netherlands
501	Dr. George Demetri	Harvard Medical School	Boston, MA	USA
503	Dr. Bart Barlogie	University of Arkansas for Medical Sciences	Little Rock, AR	USA
504	Dr. Michael Heinrich	Oregon Health Sciences Univ	Portland OR	USA
505	Dr. Robert Shepard	UVA Health System	Charlottesville VA	USA
601	Prof. Heikki Joensuu	Helsinki University Central Hospital	Helsinki	Finland
701	Dr. Denis Soulieres	Centre Hospitalier Universitaire de Montreal	Montreal (Quebec)	Canada
702	Dr. Hal Hirte	Hamilton Regional Cancer Centre McMaster University Medical Centre	Hamilton Ontario	Canada
801	Dr. Richard Herrman	Unikliniken Kantonsspital Basel	Basel	Switzerland
901	Dr. Grant McArthur	Peter MacCallum Cancer Institute	Melbourne	Australia

Demographics, karyotype and number of prior therapies for Study B2225 MDS/MPD patients are summarized in **Table 5.**

Table 5: Demographics –MDS/MPD patients

Patient or Reference		Age	Sex	Race	Karyotype	No. of previous therapies
GBR/201/004*	B2225	20	M	Caucasian	t(5:12) (q33:p13)	1
GBR/201/005*	B2225	51	M	Caucasian	t(5:12) (q33:p13)	0
GBR/201/073	B2225	56	M	Caucasian	NE	0
AUS/901/177	B2225	57	F	Caucasian	t(5:12)	1
CHE/801/045	B2225	42	F	Caucasian	Normal	2
AUS/901/139	B2225	86	F	Caucasian	Normal	1
GBR/201/089	B2225	72	F	Caucasian	t(1:3:5)	8
Apperley, et al (2002)		36	M	Unk	t(5:12)(q33:p13)	>1
Apperley, et al (2002)		69	M	Unk	t(5:12)(q33:p13)	0
Wilkinson, et al (2003)		2	F	Unk	t(1:5)(q23:q33)	1
Vizmanos, et al (2004)		35	M	Unk	t(5:14)(q33:24)	1
Grand, et al (2004)		79	M	Unk	t(5:15)(q33:q22)	>1
Levine, et al (2005)		42	M	Unk	t(5:14)(q33:q32)	0
Magnusson, et al (2002)		29	M	Hispanic	t(5:17)(q33:p13.3)	0
Pitini, et al (2003a)		68	M	Unk	t(5:12)(q33:p13)	0
Wittman, et al (2004)		2	F	Unk	t(5:12)(q33:p13)	0
Garcia, et al (2003)		44	M	Unk	t(5:10)(q33:q22)	0
Trempat, et al (2003)		47	M	Unk	t(4:22)(q12:q11)	>1
Safley, et al (2004)		57	M	Unk	t(4:22)(q12:q11)	1
Cortes, et al (2003) (10pts)		48-73	NA	Unk	No t5q33 or t4q12	NA
Pardanani, et al (2003)		45	M	Unk	Normal	1
Pardanani, et al (2003)		58	M	Unk	Trisomy 8	>1

* Patients number 2 and 4 reported by Apperley et al (2002)

Among the 7 patients with MDS/MPD in study 2225 there were 3 CRs (43%), 1 PR (14%) 2 PD (29%) and 1 non-evaluable patient because of missing data (**Table 6**).

To clarify the sponsor's presentation of efficacy data the FDA reviewer's questions to the sponsor and the sponsor's reply are provided in the following paragraphs.

Question from FDA Regarding B2225 patients

On January 5, 2006 the following e-mail question was received from FDA. "We are having a hard time confirming responses of the 7 MDS/MPD patients in study B2225 using the submitted datasets. Please provide serial hematology and bone marrow data for each of the 7 patients"

Novartis responded to the above question on January 12, 2006 via e-mail with references to the various datasets within their submission pertaining to these seven patients.

On January 13, 2006 the following additional e-mail question was received from FDA:

"We still cannot confirm responses of MDS/MPD patients. The patient data in the BMA database does not include all of the dates listed in Appendix 7.1, pages 615-616 or 1168, or pages 90-91. The hematology results from Appendix 7.1 do not specifically identify MDS/MPD patients."

Sponsor's Reply

Study B2225

Study B2225 is an open label, multicenter, phase II clinical trial testing the efficacy and safety of imatinib in patients suffering from life threatening diseases associated with Abl, Kit or PDGFR PTK and the disease was refractory to standard therapeutic options or for which no conventional therapies of definitive benefit existed. The primary objective of the study was to assess the efficacy of imatinib in patients suffering from different malignancies known to be associated with one or more imatinib-sensitive TKI following failure of standard therapeutic options or without therapeutic options of definitive benefit.

The secondary objectives were to assess the safety and tolerability of imatinib, to evaluate the pharmacokinetic (PK) profile of imatinib in selected patients and to assess, if feasible, the functional significance of relevant signal-transduction components in target tissues by evaluating the expression and activation status of the relevant TK molecules or associated signaling molecules, by measuring indices of cellular proliferation and by correlating the changes in the above findings with clinical outcomes. However, due to the inconsistent collection of biological samples, these latter secondary objectives were not evaluated.

Five to ten patients per indication, condition, or disease were initially enrolled. Lack of clinical efficacy coupled with lack of demonstration of any surrogate pharmacodynamic effect (e.g. target PTK inhibition in the first 5 patients) excluded future patients with the same indication, condition or disease from the study.

Further comments:

The B2225 trial was initially designed as an exploratory trial and not a registration trial in its beginning. The rarity of the diseases was previously known, but the ability of a clinical trial to attract such patients was not known. As patients were registered into the trial it was also apparent that in certain diseases, such as MDS/MPD, remarkable clinical responses to imatinib were being seen by the investigators. Due to the rarity of the diseases and the responses noted, Novartis decided to submit the results to the health authorities of B2225 as Novartis was doubtful that an additional trial could be accomplished in a reasonable timeframe. The registration strategy combining data from the B2225 trial and publications was agreed with the FDA during the EOP1-2 meeting on August 12, 2004. However, some caveats regarding the trial are relevant to the reviewers.

The CRFs are designed for the trial as a whole and not specifically for the indication MDS/MPD. The response criteria are broad SWOG response criteria and not specific to acute leukemias. For a hematology disorder such as MDS/MPD the basis for response is based on normalization of the peripheral blood count and bone marrow. The CRFs in the trial are basic and this results in:

Hematology CRFs that do not specifically request a differential that includes abnormal circulating forms, such as blasts. The CRF accurately requests hemoglobin, total WBC, platelet determinations and WBC differential count, but abnormal cells must be mentioned in "Other" on the differential count and placed into a comment section. Understandably this was not always done by study personnel.

Similarly, the CRFs relevant to bone marrow analyses requested the type of procedure, aspiration results and biopsy results. There are places on the assessment form to record abnormalities, but again there is no specific request to comment on cytogenetics, etc. that would be most relevant to an MDS/MPD population of patients. Again, study personnel must enter specific comments relevant to these patients to accurately capture bone marrow data on patients with MDS/MPD. This would require disease specific knowledge and expertise the person filling out the form may not have possessed.

The CRFs relevant to assessment of tumor responses are not leukemia specific and do not require simultaneous listing of either hematological or bone marrow assessments to code an assessment of tumor response. The only objective response assessment on the CRFs allowed was CR, PR, SD/No response, PD, or Unknown. Comments were optional but could be made. As stated in the Clinical Overview cytogenetic response was not a requirement for the determination of response in Study B2225, but was often evaluated in these patients. In fact, a complete cytogenetic response is reported in the two cases published by Apperley, et al (2002).

2. Further data capture for this trial, as Novartis prepared for submission, was retrospective, on paper forms, and performed by a CRO.

Despite the data capture difficulties of B2225 mentioned above Novartis feels that the responses claimed in the submission dossier from B2225 are accurate and documented in our submission. Each of the investigators caring for these rare patients is an outstanding expert in the management of patients with leukemias and myelodysplastic disorders and in conducting an overall assessment of the patient's response to imatinib during the trial. To assist the reviewers Novartis has compiled below a summary of each patient and referenced the results to specific page listings in the filed appendices. Results are documented as to the date and visit when a normalization of the blood count was obtained, data on bone marrow assessments performed, and added the investigator comments for each case relevant to response determination.

Sponsor patient evaluations are as follows:

6 Page(s) Withheld

√ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

Table 8: Literature References-MDS/MPD with PDGFR gene rearrangements

Reference	Karyotype	Daily Dose (mg)	Hematological response	Cytogenetic response	F/U (mo)
Apperley, et al (2002)	t(5:12)(q33:p13)	400	Complete	Complete	13+
	t(5:12)(q33:p13)	400	Complete	Complete	12+
Wilkinson, et al (2003)	t(1:5)(q23:q33)	NA	Complete	Major	7+
Vizmanos, et al (2004)	t(5:14)(q33:24)	200–400	Complete	Complete	6+
Grand, et al (2004)	t(5:15)(q33:q22)	300–400	Partial	ND	5
Levine, et al (2005)	t(5:14)(q33:q32)	400	Complete	Complete	18+
Magnusson, et al (2002)	t(5:17)(q33:p13.3)	400	Complete	Complete	6+
Pitini, et al (2003a)	t(5:12)(q33:p13)	400	Complete	Complete	10+
Wittman, et al (2004)	t(5:12)(q33:p13)	200	Complete	Complete	4+
Garcia, et al (2003)	t(5:10)(q33:q22)	400	Complete	Complete	12+
Trempat, et al (2003)	t(4:22)(q12:q11)	400	Complete	Partial	3+
Safley, et al (2004)	t(4:22)(q12:q11)	100	Complete	ND	7+
Cortes, et al (2003) 10 patients	No t5q33	400	None	None	NA
Pardanani, et al (2003a)	Normal	100	Partial	NA	5+
	Trisomy 8	400	None	None	1

Reference case summary

Apperley, et al (2002) describe imatinib treatment in four patients with myeloproliferative diseases with PDGFRβ gene re-arrangements. Two of these patients (No. 2 and 4 in the publication) were treated in the context of [Study B2225]. Three of the four patients presented with leukocytosis and eosinophilia and were noted to carry the ETV6-PDGFRβ fusions gene and t(5:12)(q33:p13) translocation. The fourth patient also had leukocytosis and eosinophilia, but had a t(5:12) translocation involving PDGFRβ with an unknown partner gene. Each patient was treated with imatinib 400 mg/day. Two of the patients had previously been treated with hydroxyurea and interferon-α with minimal benefit. In all four patients, a normal blood count was achieved within 4 weeks of initiation of imatinib therapy. Patient No. 4 had involvement of the skin, and the lesions began to resolve shortly after treatment began. The t(5:12) translocation was undetectable after 4 weeks in one patient (No. 4), after 12 weeks in 2 patients (No. 2 and 3) and after 9 months in patient No. 1. In the three patients with the ETV6- PDGFRβ fusion gene, the transcript level decreased, and in one patient, it became undetectable by 36 weeks. All clinical responses were durable at 9 to 12 months of follow-up.

Wilkinson, et al (2003) describe a 2 year old girl diagnosed at 11 months with MDS/MPD with eosinophilia that was refractory to etoposide, cytarabine, and interferon. Cytogenetics revealed a t(1:5)(q23:q33) translocation in 100% of bone marrow metaphases. Molecular diagnostic techniques confirmed a novel gene fusion of PDE4DIP to PDGFRβ. Imatinib was initiated based on the activation of PDGFRα found in cases of hypereosinophilic syndrome successfully treated with imatinib (Cools, et al 2003), suggesting that activation of the PDGFR receptor tyrosine kinase family was a common theme in that phenotypically similar collection of diseases. Once imatinib was initiated, complete clinical remission and CHR, as well as major cytogenetic response, were achieved.

Vizmanos, et al (2004) describe the case of a patient with an eosinophilic myeloproliferative disorder with PDGFRβ involvement. A 35 year old male with a longstanding chronic myeloproliferative disorder was found to have PDGFRβ fusion associated with a t(5:14)(q33:q24) translocation and NIN as the partner gene. The patient had previously been treated with interferon-α and hydroxyurea with limited success, but was initiated on imatinib once the PDGFRβ re-arrangements was noted. The patient did not tolerate 400 mg/day of imatinib, but when the dose was initiated at 200 mg/day hematological and cytogenetic remission occurred, lasting for at least 7 months, from April to November 2003. At that time the patient was found to be still RT-PCR positive, which prompted an increase of the imatinib dose to 400 mg/day in an attempt to promote molecular remission, but further patient data are not described in the case report.

Grand, et al (2004) describe a case of imatinib-responsive eosinophilic MPD with PDGFRβ gene re-arrangement. This case involved a 79 year old male who presented with constitutional symptoms, rash, leukocytosis, and splenomegaly, with the later development of thrombocytopenia and anemia. Initially a CML diagnosis was made, but the patient's bone marrow was negative for the Philadelphia chromosome and Bcr-Abl re-arrangements. A t(5:15)(q33:q22) translocation was identified as well as a novel fusion of TP53BP1 to PDGFRβ. The patient was initially treated variously with hydroxyurea, interferon-α, busulfan, and mercaptopurine with some resolution of leukocytosis and skin infiltrations, but the responses were transient. Imatinib was initiated at 400 mg/day after identification of the PDGFRβ re-arrangement and the in vitro sensitivity described previously in this report. The leukocyte count initially declined from 27 × 10^9/L to the normal range within 9 days and the spleen size decreased from 20 to 15 cm. During imatinib treatment the platelet count improved as well, with a reduction of platelet transfusion from alternate days to weekly, but neutropenia developed and the imatinib was reduced to 300 mg/day, and then interrupted by additional episodes of neutropenia. After 5 months of therapy, resistance to imatinib developed which could not be overcome by dose escalation and the patient died of intracerebral hemorrhage with severe thrombocytopenia.

Levine, et al (2005) describe a patient with an MPD associated with a novel PDGFRβ fusion gene partner. This case involved a 42 year old man with a myeloproliferative

diseases characterized by a t(5:14)(q33:q32) translocation and a KIAA1509-PDGFRβ gene fusion. The patient had leukocytosis and his bone marrow biopsy revealed a hypercellular marrow with granulocytic hyperplasia, but no lymphadenopathy or splenomegaly was present. The patient was treated with imatinib 400 mg/day on the basis of the PDGFR re-arranged myeloproliferative diseases. Imatinib therapy resulted in rapid normalization of the patient's blood counts, and subsequent bone marrow biopsies and karyotypic analysis were consistent with sustained complete remission. Remission persisted for more than 18 months.

Magnusson, et al (2002) report a 29 year old Hispanic male patient with CMML in molecular relapse after a bone marrow transplant responding to treatment with imatinib. Cytogenetic analysis revealed a t(5:17)(q33:p13.3) translocation and the rabaptin-5-PDGFRβ (RAB5EPPDGFRβ) fusion oncogene was cloned from the patient's blood cells. The patient was started on 400 mg/day imatinib. Four weeks after initiation of imatinib therapy, molecular testing for RAB5EP-PDGFRβ showed marked reduction in the expression of the RAB5EP-PDGFRβ fusion transcript in peripheral blood cells, and by 6 weeks after starting the drug the patient had attained molecular remission. He tolerated therapy well, without any side effects. No myelosuppression was noted. Six months after initiating imatinib therapy, he continued to be in molecular remission.

Pitini, et al (2003a) describe the case of a 68 year old male diagnosed with MPD-MDS with typical t(5:12)(q33:q13) translocation who responded to 400 mg/day imatinib with normalized blood count at 3 weeks and complete cytogenetic response (CCR) at 16 weeks after treatment initiation. He tolerated therapy well, without any side effects. The response was durable without any side effects at 10 months of imatinib therapy.

Wittman, et al (2004) reported the results of imatinib treatment in a 2 year old female patient with atypical chronic myeloid leukemia (aCML). Cytogenetics revealed a t(5;12)(q33:p13) translocation with a corresponding fusion gene ETV6-PDGFRβ. This patient presented with congestive heart failure and massive hepatosplenomegaly, leukocytosis (WBC = 209 × 10^9/L), anemia (hematocrit = 18%) and thrombocytopenia (14 × 10^9/L), increased eosinophils (9%), but relatively few monocytes (5%). Limited treatment with hydoxyurea achieved a PR that lasted approximately 6 months. After PD despite increased doses of hydoxyurea, treatment with imatinib was initiated at 200 mg/day (approx. 340 mg/m^2). At this dose, CHR was achieved within 1 month, and CCR by 4 months. Her cardiac disease, which was deemed to be the result of hypereosinophilia, nearly resolved with imatinib. There were no obvious side effects. An unrelated donor BM transplant was performed at this point. Unfortunately, the transplant was complicated by steroid refractory acute graft vs. host disease, and the patient died of transplant-related complications approximately 7 months after transplant.

Garcia, et al (2003) report a 44 year old man with atypical CML and a t(5:10)(q33:q22) translocation. This patient presented with leukocytosis and splenomegaly. The WBC was

158 x 10⁹/L, hemoglobin level was 91 g/L and platelet count was 352 x 10⁹/L. Analysis of peripheral blood (PB) smear revealed a remarkable dysplasia in myeloid cells. The patient started imatinib treatment at 400 mg/day and complete clinical and cytogenetic responses were achieved after 3 weeks of therapy. At 8 weeks, RT-PCR analysis showed a 99% reduction in H4/PDGFRβ expression in PB compared with blood samples taken prior to treatment. The patient remained in CR after one year of therapy.

Cortes, et al (2003) have treated three patients with CMML and 7 patients with Ph negative CML with no detectable PDGFRβ fusion gene or eosinophilia with 400 mg/day imatinib without any significant response. One patient with CMML had stable disease for 33 weeks and another who did not achieve CHR after 4 weeks on therapy had evident reduction in spleen size (from 9 to 5 cm BCM).

Pardanani, et al (2003a) present 2 male patients with what was described as an eosinophilia associated chronic myeloid disorder (CMD). In these cases none of the known mutations in cellular targets of imatinib (Bcr-Abl, C-Kit, or PDGFRβ tyrosine kinases) were identified. The first patient was a 45 year old male with a 20 year history of untreated eosinophilia who developed splenomegaly, leukocytosis, and rapid clinical decline. The patient was started on imatinib 100 mg/day and experienced a dramatic response with clinical and histologic remission of disease. The second patient was a 58 year old male who developed an eosinophilic CMD with splenomegaly and a pure red cell aplasia. Corticosteroids, hydoxyurea and cyclosporine were used and produced temporary clinical response before the disease progressed. Imatinib was initiated at 400 mg/day, but the patient failed this therapy as well.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

The current submission includes efficacy data for 7 patients with MDS/MPD treated in an open label, multicenter, Phase II clinical trial (study B2225) and a further 24 patients with MDS/MPD who were summarized in 13 published studies. Of the total 31 patients, 4 study B2225 patients and 10 literature patients had a chromosome 5 translocation presumably involving PDGFRβ and 2 literature patients had a chromosome 4 translocation presumably involving PDGFRα. Of the 4 B2225 patients with a chromosome 5 translocation imatinib treatment produced complete hematologic and cytogenetic responses in 2 patients and a long duration partial response in a third patient. The fourth patient was non-evaluable for response. One additional B2225 complete responder had a non-evaluable karyotype. Of the 10 literature patients with a chromosome 5 translocation 9 had complete haematological responses of 4+ months to 18+ months duration (median 11+ months). Eight of these patients also had a complete cytogenetic response and the remaining patient had a major cytogenetic response. Of the 2 literature patients with a chromosome 4 translocation both had complete hematologic

responses of 3+ months and 7+ months duration with imatinib treatment. Of the 2 imatinib treated B2225 patients who had a normal karyotype and the 12 literature patients without a chromosome 5 translocation there was only 1 partial hematologic response.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology and chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsened after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form only if the patient received study treatment. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy, when they were recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Any Adverse Event occurring after the study completion and within four weeks of last drug intake was recorded on the Adverse Event CRF page.

Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also had to be reported to Novartis within 24-hours of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:
1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. was significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any pregnancy or fathering the child during the study will be considered as an SAE for the purpose of study reporting.

Events not considered serious are hospitalizations occurring under the following circumstances: planned before entry into the clinical study; for elective treatment of a preexisting hospitalization (unless fulfilling the criteria above); routine treatment or monitoring of the study indication and not associated with any deterioration in condition.

Any SAE occurring within four weeks after completion of the study has to be reported and recorded. In addition any pregnancy within 84 days (12 weeks, 3 months) after the last STI571 intake has to be reported and recorded as an SAE.

The institution performed laboratory analyses according to the Visit Schedules.
At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page in addition to the appropriate laboratory CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF. AE's are summarized in **Table 8**.

Table 9: Adverse events regardless of study drug relationship

Primary System Organ Class Preferred Term –Total	**7**	**(100.0)**
Blood and lymphatic system disorders-Total	4	(57.1)
Anemia	2	(28.6)
Febrile Neutropenia	1	(14.3)
Neutropenia	1	14.3)
Pancytopenia	1	(14.3)
Thrombocytopenia	1	(14.3)
ALT increase	1	(14.3)
Eye disorders-Total	1	(14.3)
Eye edema	1	(14.3)
Lacrimation increased	1	(14.3)
Gastrointestinal disorders -Total	5	(71.4)
Nausea	4	(57.1)
Diarrhea	3	(42.9)
Abdominal distension	1	(14.3)
Abdominal pain	1	(14.3)
Abdominal pain lower	1	(14.3)
Abdominal pain upper	1	(14.3)
Constipation	1	(14.3)
General disorders and administration site conditions - Total	4	(57.1)
Fatigue	2	(28.6)
Catheter site pain	1	(14.3)
Chest pain	1	(14.3)
Edema	1	(14.3)

Edema peripheral	1	(14.3)
Pyrexia	1	(14.3)
Infections and infestations -Total	3	(42.9)
Fungal infection	1	(14.3)
Oral candidiasis	1	(14.3)
Oral infection	1	(14.3)
Pseudomonas infection	1	(14.3)
Respiratory tract infection fungal	1	(14.3)
Subcutaneous abscess	1	(14.3)
Wound infection pseudomonas	1	(14.3)
Injury, poisoning and procedural complications-Total	3	(42.9)
Blood blister	1	(14.3)
Contusion	1	(14.3)
Eye injury	1	(14.3)
Foot fracture	1	(14.3)
Skin laceration	1	(14.3)
Investigations-Total	1	(14.3)
Weight increased	1	(14.3)
Metabolic and Nutritional-Total	2	(28.6)
Anorexia	1	(14.3)
Fluid retention	1	(14.3)
Musculoskeletal-Total	4	(57.1)
Muscle cramp	3	(42.9)
Arthralgia	2	(28.6)
Bone pain	1	(14.3)
Myalgia	1	(14.3)
Pain in extremity	1	(14.3)
Nervous System disorders-Total	1	(14.3)
Dizziness	1	(14.3)
Psychiatric disorders-Total	1	(14.3)
Depressed mood	1	(14.3)
Panic attack	1	(14.3)
Renal and urinary disorders-Total	1	(14.3)
Renal tubular disorder	1	(14.3)
Respiratory, thoracic and mediastinal disorders -Total	2	(28.6)
Crackles lung	1	(14.3)
Dyspnea	1	(14.3)
Skin and subcutaneous tissue disorders -Total	4	(57.1)
Periorbital edema	2	(28.6)
Face edema	1	(14.3)
Rash	1	(14.3)

7.1.1 Deaths

No patient with MDS/MPD, died on study. Patient [201/089], a 69-year old woman with MDS/MPD, died of Pseudomonas aeruginosa infection approximately 3 months after having interrupted imatinib treatment due to CTC grade 1 pancytopenia (CTC grade 3 neutropenia was also observed), from which she recovered. This patient was heavily pretreated with 8 different chemotherapeutic regimens administered from 1996 to the study start in May 2002.

7.1.2 Other Serious Adverse Events

Four patients experienced non-fatal SAEs. Patient [201/004] had a Pseudomonas wound infection, patient [201/089] had fever, skin rash, fungal infection and renal tubular damage, patient 801/45 had a gluteal abscess and febrile neutropenia and patient [901/139] had a left pre-tibial laceration and anemia.]

7.1.3 Dropouts and Other Significant Adverse Events

Two patients discontinued therapy; patient 201/089 above and patient 801/045 who developed grade 2/4 cramps and arthralgia.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

See Table

7.1.6 Laboratory Findings

See Table

7.1.7 Vital Signs

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

7.1.8 Electrocardiograms (ECGs)

No ECGs were performed for the MDS study.

7.1.9 Immunogenicity

There is no new relevant information.

7.1.10 Human Carcinogenicity

There is no new relevant information.

7.1.11 Special Safety Studies

There is no new relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Gleevec has no known potential for abuse..

7.1.13 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
- PSUR 7 covering the period 11 May 2005 - 10 May 2006
- 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 "Sweet's Syndrome" was proposed for inclusion to the BPI.

In 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 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.

In PSUR 7 and in a recent literature report congestive heart failure and left ventricular dysfunction associated with Gleevec treatment were updated. A recent article published online in Nature Medicine (Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine; advance online publication July 23rd. 2006) reported 10 Gleevec treated patients who developed severe congestive heart failure and left ventricular dysfunction. Supplemental data available on the Nature Medicine website show that prior to Gleevec treatment all 10 patients had New York Heart functional class 1 and normal left ventricular ejection fractions. Some of these patients had pre-existing conditions including hypertension, diabetes and coronary artery disease. In an abstract published in the Journal of Cardiac Failure (Iliescu C, Wamique Yusuf S, Auerbach L, et al. Impact of angiotensin converting enzyme inhibitors & carvedilol on recovery of cardiac function in imatinib associated cardiomyopathy. Journal of Cardiac Failure 2005; 40 No. 6 Suppl. Abstract 054. 9th Annual Scientific Meeting of the Heart Failure Society of America, Sept 18-21st 2005) the authors stated that treatment with angiotensin converting enzyme inhibitors (ACE-I) and carvedilol resulted in significant improvements in left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) Class. Three of these patients, when re-challenged, were reported to have no further diminution of cardiac function.

The Nature Medicine article also reports on preclinical studies showing that Gleevec treated mice develop left ventricular contractile dysfunction. Gleevec also induces cell death in isolated cardiomyocytes. The authors hypothesize that development of cardiac dysfunction is related to inhibition of the Abl receptor and may be a possibility with any drug that targets the Abl receptor.

A thorough review of the sponsor's safety database yielded 148 spontaneous cases of cardiac events. The median age was 65 years. Of 117 patients with sufficient clinical information for analysis approximately 50% had a history of cardiovascular disease before the onset of Gleevec treatment (mostly hypertension and ischemic heart disease), 40% were on cardiac medications and 8.5% experienced worsening of preexisting heart disease.

Thus heart failure is a recognized, potentially severe, but uncommon complication of Gleevec therapy. Current information does not support routine screening and monitoring of cardiac function in patients taking Gleevec. Any patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with symptoms consistent with cardiac failure should be aggressively evaluated and treated.

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

The protocol specified Gleevec dose for the 7 MDS/MPD patients was 400 mg/day. The dose received is summarized in **Table 10**.

Table 10: Dose intensity (mg/day)

Myeloproliferative disorder	(N=7)
Mean ±SD	433.1 ±275.36
Median	395.7
Min - Max	50.8 - 880.5

Reasons for dosage change are listed in **Table 11**.

Table 11: Dosage change reason

Myeloproliferative disorder	7 (100)
Adverse event	2 (28.6)
Dosing error	1 (14.3)
Lab or test abnormality	1 (14.3)

The fact that only 7 patients were studied limits the conclusions that can be drawn.

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 drug related AEs occurred in 2%, of patients in chronic, phase CML. 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). Gleevec associated myelosuppression was 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. The data indicate that the drug is well tolerated in the target population.

The currently reported AE's in patients with MDS/MPD are similar to the above known Gleevec adverse effects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Separate safety data was provided for each study. Because of different Gleevec doses for solid tumors and hematologic malignancies, because of the small number of patients studied for each disease and because of the large amount of safety data already available it was not felt to be worthwhile to pool safety data. .

7.4.2 Explorations for Predictive Factors

Predictive factors including dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions were not explored in the current study.

7.4.3 Causality Determination

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

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 with MDS/MPD 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.

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

In accordance with 21 CFR 314.55 the sponsor requests a full waiver of the requirements for submission of data that are adequate to assess the safety and efficacy of Gleevec in this population of pediatric patients. The basis for this waiver is 314.55c(2)(ii): necessary studies are impossible or highly impractical because the number of patients is so small. To our best knowledge, there is no published information on the frequency of Myeloproliferative Diseases (MPDs) associated with PDGFR gene re-arrangements. The lack of a standardized disease code precludes an automatic search in health databases. In addition, there is no population-based registry allowing estimation of the incidence and prevalence of the disease. The diagnosis seems to be very rare, with only a small number of case reports published to date.

8.5 Advisory Committee Meeting

An ODAC meeting to discuss this application is not planned.

8.6 Literature Review

Apperley JF, Gardembas M, Melo JV, et al (2002). Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med; 347(7):481-7.

Cortes J, Giles F, O'Brien S, et al (2003) Results of imatinib mesylate therapy in patients with refractory or recurrent acute myeloid leukemia, high-risk myelodysplastic syndrome, and myeloproliferative disorders. Cancer; 97(11):2760-65.

Garcia JL, Font de Mora J, Hernandez JM, et al (2003) Imatinib mesylate elicits positive clinical response in atypical chronic myeloid leukemia involving the platelet-derived growth factor receptor beta. Blood; 102 (7):2699-700.

Grand FH, Burgstaller S, Kuhr T, et al (2004) p53-Binding protein 1 is fused to the platelet derived growth factor receptor beta in a patient with a t(5;15)(q33;q22) and an imatinibresponsive eosinophilic myeloproliferative disorder. Cancer Res; 64(20):7216-9.

Levine RL, Wadleigh M, Sternberg DW, et al (2004) KIAA1509 is a novel PDGFRβ fusion partner in imatinib-responsive myeloproliferative disease associated with a t(5:14)(q33:q32) Leukemia; 19(1):27-30.

Magnusson MK, Meade KE, Nakamura R, et al (2002) Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor β receptor fusion oncogene. Blood; 100(3):1088-90.

Pardanani A, Elliott M, Reeder T, et al (2003a) Imatinib for systemic mast-cell disease. Lancet; 362(9383):535-6. Pardanani A, Reeder T, Porrata LF, et al (2003b) Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. Blood; 101(9):3391-7.

Pardanani A, Brockman SR, Paternoster SF, et al (2004) FIP1L1-PDGFRα fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. Blood; 104(10):3038-45.

Pitini V, Arrigo C, Teti D, et al (2003a) Response to STI571 in chronic myelomonocytic leukemia with platelet derived factor beta receptor involvement: a new case report. Haematologica 88(05):ECR18.

Safley AM, Sebastian S, Collins TS, et al (2004) Molecular and cytogenetic characterization of a novel translocation t(4:22) involving the breakpoint cluster region and platelet growth factor receptor-alpha genes in a patients with atypical chronic myeloid leukemia. Genes, Chromosomes & Cancer ; 40:44-50.

Trempat P, Villalva C, Laurent G, et al (2003) Chronic myeloproliferative disorders with rearrangement of the platelet-derived growth factor a receptor: a new clinical target for STI571/Glivec. Oncogene; 22:5702-6.

Vizmanos JL, Novo FJ, Roman JP, et al (2004) NIN, a gene encoding a CEP110-like centrosomal protein, is fused to PDGFRβ in a patient with a t(5:14)(q33:q24) and an imatinib responsive myeloproliferative disorder. Cancer Res; 64(8):2673-6.

Wilkinson K, Velloso ER, Lopes LF, et al (2003) Cloning of the t(1:5)(q23:q33) in a myeloproliferative disorder associated with eosinophilia: involvement of PDGFRβ and response to imatinib. Blood; 102(12):4187-90.

Wittman B, Horan J, Baxter J, et al (2004) A 2-year-old with atypical CML with a

t(5:12)(q33:p13) treated successfully with imatinib mesylate. Leukemia Research 28(S1):S65-9.

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 OVERALL ASSESSMENT

9.1 Conclusions

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

9.2 Recommendation on Regulatory Action

Regular approval of the proposed indication "Gleevec is indicated for the treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements." .

9.3 Recommendation On Postmarketing Actions

9.3.1 Risk Management Activity

Continue post-marketing surveillance

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

Assure availability of a validated test kit for detection of PDGFR gene rearrangement by FISH analysis. The Pre-Market Application (PMA) filing by a 3rd party should occur by 4 months after approval.

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.

10.3 DSI Inspection

The following are "preliminary results" from NEW-DO and from NYK-DO regarding the inspections of Dr. George Demetri and Dr. Richard Silver for NDA-21588/S-011 and S-013 for Gleevec®. Based on no FDA 483s issued, both sites appear to be in compliance with the applicable GCP regulations.

NWE-DO

Dr. George Demetri (Study B2225) (Site 501) (6 subjects)
DFCI & Harvard Medical School
Inspection completed on April 28, 2006.
No FDA 483 was issued. At lease two instances of minor deviations from the protocol related to the +/-2 day visit window(4 out of 6 subjects had visits outside this 2 day window) and subjects being provided much larger quantities of study medications (up to 6 month supplies were given to some subjects; the protocol required up to 6 weeks supply). However, these deviations were discussed and approved by the sponsor.

NYK-DO

Dr. Richard T. Silver (Study B2225) (Site 506) (5 subjects)
New York Hospital- Cornell
Inspection completed April 26, 2006
No FDA 483 was issued. Study records and documentations at this site were found to be highly organized; studies were meticulously monitored by the regulatory staff of Cornell and under the close supervision of the sponsor. Data listings and the reporting of AEs

and SAEs were found to be accurately reported. Drug accountability records were in good order.

I would like to forward the following additional observations made by the FDA Field Investigator related to bone marrow cytogenetic study requirement (to be done at screening and weeks, 13 and 25 per protocol). I wanted to see if you have any further issues or comments with regard to cytogenetic screening/cytogenetic response or Dr. Silver's comments about FDA requirements with regard to the following five subjects at this site:

Subject 502 ——
Review of the bone marrow analysis CRF respectively for week five dated 24 November 1999 and week nine dated 23 December 99 revealed that the bone marrow cytogenetic analysis was not done. This deviation was attributed to a dry tap during the biopsy. This observation was discussed with Dr. Silver during the inspection and at the close out discussion. However upon review of the protocol bone marrow cytogenetic studies schedule this requirement was to be done at screening and weeks, 13 and 25. There was no protocol violations listed for this subject as part of the NDA listing. b(6)

Subject 509 ——
The subject entered the study on 1/13/2000. The screening cytogenetic report dated 1/12/00 based on a specimen date of 1/6/00 reads in part, "A bone marrow sample received on 1/6/00 was clotted on arrival. Unstimulated 24-hour cultures were set up as per protocol. The cultures failed to grow." Review of the subjects medical record revealed that there was adequate documentation to support the diagnosis of the Philadelphia chromosome positive ALL. A cytogenetics report dated 5/16/00 with a specimen date of 2/14/00 utilizing fluorescent in situ hybridization (FISH) with the BCR/ABL DNA probe revealed 12.5% Ph positive and 87.5% Ph negative interfaces were found. The protocol violation section of the NDA states that subject 509 be excluded per protocol analysis (cytogenetic response) as the protocol violation reads, "Ph chromosome negative at baseline." b(6)

Subject 510 ——
The subject entered the study on 1/21/2000.
The screening cytogenetics report date 1/28/00 based on a specimen date of 1/19/00 was negative for Philadelphia positive chromosome. However, review of the medical records revealed that there was adequate documentation to indicate that the subject was clinically positive for Ph positive ALL. The protocol violation section of the NDA states that subject 510 be excluded from per protocol analysis (cytogenetic response). b(6)

Subject 526 ——
Subject entered the study on 2/17/00. The bone marrow specimen was obtained on 2/16/00. The screening bone marrow cytogenetic analysis was not done because of a dry tap bone marrow aspirate. The bone marrow specimen was only enough to be sent for b(6)

surgical pathology and not cytogenetics. The molecular pathology report date 2/15/00 based on a specimen date of 2/4/00 indicates BCR-ABL analysis consistent with a presence of a Philadelphia chromosome (t 9; 22). In addition, the cytogenetics report dated 1/13/00 based on a specimen date of 11/30/99 indicates that the Philadelphia chromosome was present in 100% of the cells studied. Lastly various components of the blood chemistry for the week one day one visit was not done.

The protocol violation section of the NDA states that subject 506 has minor protocol violations as there is no documentation of Ph chromosome positivity (Ph missing at baseline).

b(6)

Subject 520 ——
Review of the bone marrow analysis CRF respectively for week five dated 13 March 2000 revealed that the bone marrow cytogenetic analysis was not done. This observation was discussed with Dr. Silver during the close out discussion. This deviation was attributed to a dry tap during the biopsy However upon review of the protocol bone marrow cytogenetic studies schedule required this to be done at screening and weeks, 13 and 25. The blood chemistry week one day one visit two was not done as part of day one of dosage. There was no protocol violations listed for this subject as part of the NDA listing

These aforementioned observations were discussed with the regulatory coordinators during the conduct of the inspection and with Dr. Silver as noted. A close out discussion was conducted with Dr. Silver and the regulatory coordinators. No FDA 483 was issued. Dr. Silver acknowledged the inspectional findings and made comments with regard to the definitive diagnosis of Philadelphia positive chromosome as it pertains to the bone marrow cytogenetic studies and fluorescent in situ hybridization (FISH) using the BCR/ABL DNA probe. He stated that he made it very clear during the investigator meetings that they were not doing the BCR/ABL test or FISH analysis. He stated that because of this there would be deficiencies noted and he has written various articles in the literature about this. He stated that Novartis was made aware of this. However FDA considered the bone marrow cytogenetic studies as the standard. During discussions with Novartis, he made them aware that utilizing traditional bone marrow biopsies could result in dry taps because of a lack of aspirate and recommended that BCR/ABL test be used as there is a question of sensitivity utilizing bone marrow cytogenetic testing. Dr. Silver requested that I include this information as part of my report. Dr. Silver will respond to any correspondence received by FDA.

10.4 References

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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.

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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/

Martin Cohen
9/13/2006 04:01:47 PM
MEDICAL OFFICER

Kun He
9/13/2006 04:03:31 PM
BIOMETRICS

Rajeshwari Sridhara
9/13/2006 04:14:20 PM
BIOMETRICS

John Johnson
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Application Type	NDA 21-588
Submission Number	SE1
Submission Code	013 (Relapsed/refractory Ph+ ALL)
Letter Date	12/20/05
Stamp Date	12/20/05
Reviewer Name	Martin H. Cohen, M.D.
Statistician	Kun He, Ph.D.
Review Completion Date	10/27/06
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	S

Formulation

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

Dosing Regimen

b(4)

The recommended dose of Gleevec as single-agent [redacted] is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

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(s)

Proposed Indication:

Gleevec is indicated as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL.

Other indications:

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 present data to support the proposed indication: "Gleevec is indicated as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL".

The current submission includes efficacy and safety data obtained from 5 studies enrolling 443 subjects with relapsed/refractory Ph+ ALL or Ph+ LBL (lymphoid blast crisis). Of the 5 studies, two (trials 0109 and 03001) including 43 Ph+ ALL patients receiving Gleevec 600 mg/day in trial 0109 and 7 patients with Ph+ ALL/LBL receiving Gleevec ≥ 600 mg/day in study 03001 provide efficacy data. Trials AUS 01 and AAU02 demonstrate that Gleevec can be safely combined with intensive chemotherapy regimens and [redacted]. Study 0114 was an expanded access protocol. Efficacy data was limited to time to progression & overall survival. b(4)

1.1 Recommendation On Regulatory Action

The clinical reviewer recommends that Gleevec receive regular approval for the treatment of adult patients with relapsed/refractory Ph+ ALL. This is based upon the induction of both hematologic and cytogenetic responses in this patient population. For the 7 Ph+ ALL/LBC patients in the phase 1 study (03001) who received Gleevec doses of 600 mg/day or higher 3 had a complete hematologic response (CHR). For the 43 patients with Ph+ ALL treated with Gleevec 600 mg/day in the phase 2 study (0109) there were 3 confirmed CHR's (7%), 0 NEL (no evident leukemia) and 7 RTC/PR's (16%) in the sponsor analysis. In the sponsor analysis of unconfirmed hematologic responses there were 8 CHR's (19%), 3 NEL's (7%) and 13 RTC/PR's (30%). In the FDA analysis that included both confirmed and unconfirmed responses there were 8 CHR's (19%), 5 NEL's (12%) and 11 RTC's (26%).

Major cytogenetic responses (complete or partial; confirmed or unconfirmed) were seen in 15 (35%) of 43 Ph+ ALL phase 2 patients who received Gleevec 600 mg/day. Of the 15 patients with MCyR, 9 (21%) achieved CCyR (6 confirmed) and 6 (14%) had a PCyR (3 confirmed).

The median time to progression in study 0109 was 2.6 months (95% CI 1.9, 3.0). In the expanded access study 0114 the median TTP was 3.1 months (95% CI 3.0, 4.0).

Gleevec was generally well tolerated. The most frequently reported non-hematological AEs included nausea, vomiting, pyrexia and peripheral edema. In the population of older patients (≥ 55 years) the efficacy and safety results were comparable to those obtained in the younger population (< 55 years old). No new safety concerns were raised.

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.

1.23 Other Phase 4 Requests

None

1.3 Summary Of Clinical Findings

1.3.1 Overview of Clinical Program

The clinical program includes efficacy and safety data primarily obtained from one phase 2 study and supporting data from one phase 1 study. A total of 53 subjects with relapsed/refractory Ph+ALL are evaluable.

Background

Acute lymphoblastic leukemia represents 20% of adult acute leukemias. The disease has a bimodal distribution, with a peak of incidence around the age of 2-4 years (4-5 per 100,000), which decreases during later childhood, adolescence, and adulthood before a second, smaller peak occurs in patients older than 50 years (1 per 100,000). About 10,000 new cases are diagnosed in adults in Europe and about 5000 in the US each year. The annual incidence rates in Europe were 1.3 per 100,000 in men and 0.9 in women.

Philadelphia-positive ALL results from a reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11), which encodes the BCR-ABL fusion protein. The proto-oncogene ABL encodes a tyrosine-specific protein kinase, whose activity is tightly regulated. By contrast, the BCR-ABL fusion protein is a constitutive active protein kinase that alters signaling pathways which control the proliferation, survival, and self renewal of hematopoietic stem cells. With a frequency of about 25% of ALL, Philadelphia-positive ALL (Ph+ ALL) is the most common cytogenetic variant in adult ALL. Some studies suggest that the incidence of Ph+ ALL increases with age up to approximately 65 years and then decreases with an overall prevalence of 30% of ALL in the elderly, compared with 20% in younger adults.

The treatment of adult Ph+ ALL is an area of unmet medical need. Outcome with conventional chemotherapy in Ph+ ALL has been poor. Complete response rates have ranged from 54% to 90%, with median disease-free survival of 4 to 11 months and median survival of 9 to 13 months. The only potentially curative approach to ALL in general and, more specifically, to Ph+ ALL is allogeneic stem cell transplantation. Overall 3-year survival and rate can reach 40% in selected patients. Unfortunately, less than 30% of the

patients have a matched sibling donor and the median age of Ph+ ALL patients is approximately 60 years and therefore beyond the generally accepted upper age limit for a transplant (55 years). Furthermore many of these older patients cannot receive the standard ALL chemotherapy because of co-existing morbidity or adverse events that impede chemotherapy completion. Chemotherapy for ALL is also associated with a significant mortality, especially in elderly patients. Induction death rate can range from 8 to 50%, when the CR rate ranges from 31 to 85% and the median overall survival from 1 to 14 months.

1.3.2 Efficacy

For the 7 Ph+ ALL/LBC patients in the phase 1 study (03001) who received Gleevec doses of 600 mg/day or higher 3 had a complete hematologic response (CHR). For the 43 patients with Ph+ ALL treated with Gleevec 600 mg/day in the phase 2 study (0109) there were 3 confirmed CHR's (7%), 0 NEL (no evident leukemia) and 7 RTC/PR's (16%) in the sponsor analysis. In the sponsor analysis of unconfirmed hematologic responses there were 8 CHR's (19%), 3 NEL's (7%) and 13 RTC/PR's (30%). In the FDA analysis that included both confirmed and unconfirmed responses there were 8 CHR's (19%), 5 NEL's (12%) and 11 RTC's (26%).

Major cytogenetic responses (complete or partial; confirmed or unconfirmed) were seen in 15 (35%) of 43 Ph+ ALL phase 2 patients who received Gleevec 600 mg/day. Of the 15 patients with MCyR, 9 (21%) achieved CCyR (6 confirmed) and 6 (14%) had a PCyR (3 confirmed).

The median time to progression in study 0109 was 2.6 months (95% CI 1.9, 3.0). In the expanded access study 0114 the median TTP was 3.1 months (95% CI 3.0, 4.0)..

Hematologic and cytogenetic response rates and durations were comparable in patients less than or greater than 55 years of age.

1.3.4 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 600 mg/day for adult patients with relapsed/refractory Ph+ALL.

1.3.5 Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: 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.

CYP3A4 Substrates: 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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (**Table 1**) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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.

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 Abl tyrosine kinase at the in vitro, cellular, and in vivo level. The compound specifically inhibited proliferation of v-Abl and Bcr-Abl expressing cells, suggesting that it is not a general antimitotic agent. In colony formation assays using

progenitor cells ex vivo from patients with CML, imatinib showed selective inhibition of Bcr-Abl positive colonies. In addition, imatinib potently inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ), c-Kit, the receptor for stem cell factor (SCF), c-Fms, the receptor for macrophage stimulating factor (M-CSF), as well as Abl and Arg PTK. Imatinib also inhibits the cell signaling events mediated by activation of Bcr-Abl, c-Kit and the PDGF receptors. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor, insulin and phorbol esters. In vivo, the compound shows anti-tumor activity as a single agent in animal models at well tolerated doses.

2.2 Currently Available Treatment For Proposed Indication

Treatment of Ph+ ALL usually includes an induction of response, (with regimens including anthracyclines, vinca alkaloids with or without corticosteroids) followed by consolidation (with regimens containing the same type of drugs as induction plus cyclosphamide and Ara-C) and maintenance chemotherapy with 6-mercaptopurine, methotrexate with or without vincristine while a suitable donor for a bone marrow transplant is sought. If a donor is not found, maintenance is continued as long as possible. At relapse or progression, the only treatment options left are high-dose chemotherapy, or, in rare cases, a second transplant, or palliative treatment. Although clofarabine and nelarabine have been recently approved in the US for pediatric patients with relapsed/refractory ALL or T-cell ALL, the core chemotherapeutic regimens have remained essentially unchanged over the past decade.

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

The clinical results were discussed with the FDA on 12-Aug-2004. The objective of this meeting was to seek guidance for the approval of imatinib as a treatment for patients with rare malignancies carrying imatinib-sensitive targets. The FDA recognized the rarity of the targeted malignancies and accepted to consider a potential filing based upon an exploratory phase II study and published case reports/studies. Suggestions and recommendations on how to analyze and present the data were also given.

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_012\2005-12-16\

4.2 Table of Clinical Studies-Relapsed/refractory Ph+ ALL

Submitted studies are listed in **Table 2.**

Table 2: Submitted Studies

Study	Treatment	Purpose	n	Daily Gleevec dose
03001	Imatinib mono-therapy induction	Safety, efficacy Phase 1	20	300 mg to 1000 mg ≥600 mg (n=7)
0109	Imatinib mono-therapy induction	Efficacy, safety, Phase 2	56 48 Ph+ALL	400 mg to 600 mg 600 mg (n= 43)
0114	Imatinib mono-therapy induction	Safety: Efficacy data limited to time to progr-ession & overall survival	353	600 mg
AAU02	Imatinib combined with chemotherapy	Safety, efficacy	9	600 mg
AUS01	Imatinib combined with chemotherapy	Safety, efficacy	5	400 mg
Total number of patients			**443**	

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

DSI inspections will be performed.

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice. The phase II clinical study was monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

4.6 Financial Disclosures

No clinical investigators in the submitted studies are full or part-time employees of Novartis Pharmaceuticals Corporation. There were no disclosable financial arrangements or interests identified for all studies except the expanded access protocol 0114 (**Table 3**).

Financial disclosure information regarding the publications supporting this NDA submission was determined directly from the publication disclosure statements. The authors either did not describe financial interest in any of the publications or stated that they had no conflict of interest or financial interest.

Table 3: Financial Disclosure

Investigator	Center No.	Amount Disclosed	Category of Disclosure
		> $25,000	
		> $25,000	
		$30,700	
		> $25,000	

b(6)

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 is indicated as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL.

6.1.1 Methods

Phase 1 and phase 2 studies submitted by the sponsor were reviewed. See section 6.1.3.

6.1.2 General Discussion of Endpoints

Efficacy endpoints have been discussed with, and approved by, the FDA. Definitions of endpoints are summarized in **Table 4**.

Table 4: Endpoint Definitions

Complete hematologic response (CHR)
<5% blasts in BM
No blasts in PB
ANC >1.5 x 109/L and Platelets >100 x 109/L
No extramedullary involvement

No evidence of leukemia (NEL):
As for CHR, but without complete recovery of peripheral blood, i.e. 1.0 ≤ ANC < 1.5 x 10 9 /L and 20 ≤Platelets < 100 x 109/L

Return to chronic phase (RTC):
< 15% blasts in PB and BM
< 30% blasts + promyelocytes in PB and BM
< 20% basophils in PB
No extramedullary involvement other than spleen or liver

Cytogenetic response

Based on % positive cells = (positive cells / examined cells) x 100, at each bone marrow assessment the cytogenetic response was either:

- Complete: 0% Ph+ cells
- Partial: >0 - 35 % Ph+ cells
- Minor: >35 - 65 % Ph+ cells
- Minimal: >65 - 95 % Ph+ cells
- None: >95 % Ph+ cells
- Not done: < 20 metaphases were examined and/or response could not be assigned

A bone marrow sample was to be considered as assessable for cytogenetic response only if it contained ≥20 metaphases. This condition was always maintained for affirmation of **complete** response. However, an assessment of **partial** response was retained in a sample with <20 metaphases when it was immediately preceded or followed by a complete or partial response in another sample.

Duration of major cytogenetic response-

This duration was evaluated for all patients with major cytogenetic response and was defined as the time between first documented complete or partial response and the earliest of the following:

- loss of complete cytogenetic response- increase to >0% Ph+ cells.
- loss of partial cytogenetic response -increase by ≥30% Ph+ cells compared to lowest value before current assessment or an increase to ≥65% Ph+ cells
- discontinuation due to unsatisfactory therapeutic effect or death.

6.1.3 Study Design

Controlled Studies

No controlled studies were performed in the population of relapsed/refractory patients with Ph+ALL. **Table 5** summarizes Gleevec monotherapy trials.

Table 5: Relapsed/refractory Ph+ALL-Gleevec monotherapy trials

Study	Study objective; population	Study design	Patients	Dose regimen	Efficacy endpoint
03001	efficacy/safety; Ph+ ALL or CML-LBC	Phase I, dose escalating pilot study	Total: 20 Ph+ALL n=10 (6 adult) CML-LBC n=10	imatinib: 300-1000mg ≥600 mg (n=7)	Anti-leukemic activity by decrease in peripheral WBC counts and percent Ph+ cells in bone marrow
0109 Ph+ ALL	efficacy/safety; Ph+ ALL or CML-LBC	Open label, non randomized, multi-center, Phase II study	Ph+ALL: n=48; CML-LBC: n=8	imatinib: 400 mg (n=5) 600mg(n=43)	Confirmed hemato-logical response, response duration, cytogenetic response
0114 Ph+ ALL	Safety, expanded access program in Ph+ALL	Phase II, multi-center,	353	600 mg daily	Time to progression

Study 0114 An expanded access protocol of STI571 in adult patients with either chronic myeloid leukemia in accelerated phase or Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). The objective was to provide patients with Ph+ CML in accelerated phase (AP) or relapsed/ refractory Ph+ ALL with expanded access to STI571 until the product was commercially available. There were 353 patients with relapsed/ refractory Ph+ALL enrolled in the study. Due to the nature of this study no primary efficacy variables were to be analyzed. However, all data available from Ph+ ALL patients were used to perform Kaplan-Meier estimates of the overall survival as well as of the time to disease progression. Regarding safety all SAEs and AEs were reported, as received.

However due to the expanded access these data should be interpreted with caution as AE reporting might have been incomplete. The estimated probability [95% CI] of being alive with Ph+ALL was 44.2% [27, 62] at 12 months in patient < 55 years old and was 38.4% [20, 56] in the older patient population (≥ 55 years old). The median survival was 8.9 months with 95% CI =[7, NA] in patients ≥ 55 years old and 11.4 months with 95% CI =[6, NA] in patients < 55 years old. The estimated proportion [95% CI] of patients without progression was 11.9% [4, 20] at 12 months in patient < 55 years old and was 14.4% [5, 24] in the population of older patients (≥ 55 years old). The median time to progression was 3.1 months with 95% CI = [3, 4] in patients ≥ 55 years old and was similar in the younger patient population.

FDA Comment: *There are only 45 adult relapsed/refractory Ph+ALL patients who received the recommended Gleevec dose of 600 mg/day. (2 in study 03001 and 43 in study 0109). The 353 patients in the expanded access program are not fully evaluable for efficacy as study 0114 provides no information on response rate or duration. TTP data is likely unreliable since an evaluation schedule was not specified.*

Uncontrolled trials of Gleevec in combination with chemotherapy in patients with relapsed/refractory Ph+ALL are summarized in **Table 6.**

Table 6: Relapsed/refractory Ph+ALL-Gleevec plus Chemotherapy

Study	Study objective; population	Study design	Patients	Dose regimen	Efficacy endpoint
AAU02/ CMLALL1	efficacy/ safety; CML-BC or Ph+ ALL	Open-label, non-randomized, phase II pilot study; imatinib + induction chemotherapy	24	Pre-phase: imatinib: 600 mg daily for 7 days Induction therapy: arm 1, arm 2, arm 3	Hemato-logical + cytogenetic response
Arm 1	CML-MBC		3	idarubicin 12 mg/m2 iv days 1-3 + cytarabine 200 mg/m2 iv days 1-7 + imatinib 600 mg days 1-7	
Arm 2	CML-LBC or relapsed Ph+ ALL		9	as arm 1 plus vincristine 2 mg iv d1, d8, d15, d22 + prednisone 40 mg/m2 po d1-d28 + imatinib 600 mg d1-d7	
Arm 3			12	Protocol LALA 94	
AUS01	De-novo Ph+ ALL efficacy/ safety in Ph+ ALL	Phase II study of imatinib combined with intensive hyper-CVAD chemotherapy in patients with Ph+ALL	Total: 32 de-novo Ph+ ALL: 21; refractory Ph+ ALL: 5; Ph+ALL in CR: 6	hyper-CVAD regimen CTX 300mg/m2 on d1-d3; vincristine 2mg d4 and d11; doxorubicin 50 mg/m2 d4 and dexamethasone 40mg daily on d1-d4 and d11-d14 imatinib 400 mg qd	Hemato-logical, cytogenetic + molecular response rates, event free survival, survival

FDA Comment: *Neither of these 2 studies isolate Gleevec effect. See section 10.1 for a summary of these trials.*

Sources of pediatric efficacy data are summarized in **Table 7**.

Table 7: Sources of pediatric efficacy data

Source	Objective, population	Study design	Patients	Dose regimen	Efficacy endpoint
03001	Efficacy/safety in pediatric relapsed or refractory Ph+ALL or CML-LBC	Phase I, dose escalating pilot study	Ph+ ALL: 4 CML-LBC: 1	125 to 425 mg/m2	Anti-leukemic activity by decrease in peripheral WBC counts and percent Ph+ cells in bone marrow
Champagne 2004	Efficacy/safety in pediatric refractory or recurrent Ph+ leukemias	Phase I study in children with Ph+ leukemia	Ph+ ALL: 10	260 to 570 mg/m2	Morphologic response, hematologic response, cytogenetic response

FDA Comment: *Study There were a total of 14 pediatric patients with relapsed/refractory pediatric Ph+ALL.*

6.1.4.1 Efficacy Findings

Study 0109

Table 8 indicates 0109 study patient demographics, disease history and patient characteristics at baseline. There were 43 patients who received Gleevec 600 mg daily and 5 who received Gleevec 400 mg daily.

Table 8: Demographics, disease history and patient characteristics at baseline

Characteristics	ALL, n = 48
Age, yrs	
Median (range)	50 (22-78)
Sex, no. (%)	
Male	24 (50)
Female	24 (50)
ECOG score, no. (%)	
0-1	26 (54)
2	19 (40)
3	1 (2)
NA	2 (4)
Prior response, no. (%)	
Relapsed after first remission	19 (40)
Relapsed after 2 or more remissions	12 (25)
Refractory	17 (35)
Prior BMT, no. (%)	10 (21)
Diagnosis to study entry, mo	
Median	8
Range	2-118
WBC (x 109/L)	
Median	10
Range	0.2-195
Platelets (x 109/L)	
Median	32
Range	1-1715

Table 9 presents individual patient data of the 43 subjects enrolled into trial 0109 who were treated with Gleevec 600 mg/day and **Table 10** provides response rate and response duration data.

2 Page(s) Withheld

√ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

Table 10: FDA Response evaluation Gleevec 600 mg/day

Country/ Center/ Subject	Best response	First day of response	Last day of response	Response duration (days)
DEU/003 0511	RTC	3/31/00	5/26/00	56
DEU/004 0512	NR	-	-	
DEU/010 0509	NR			
DEU/010 0512	NR			
DEU/010 0514	CHR	3/27/00	6/27/02	822+
DEU/010 0515	NR			
DEU/010 0516	NR			
DEU/010 0517	CHR	4/20/00	4/20/00	1+
DEU/010 0518	RTC	4/28/00	5/26/00	28
DEU/010 0519	RTC	4/27/00	4/27/00	1+
DEU/010 0520	RTC	5/2/00	6/2/00	31
DEU/010 0521	NR			
FRA/001 0503	NEL	4/3/00	5/2/00	29
FRA/001 0506	NR			
FRA/001 0507	CHR	6/8/00	7/6/00	28
FRA/001 0508	RTC	5/15/00	6/13/00	29+
FRA/001 0509	NEL/CHR	6/14/00	8/8/00	55
GBR/008 0511	NEL	2/28/00	4/3/00	35
GBR/008 0515	NR			
GBR/008 0519	NR			
GBR/008 0520	RTC/NEL	5/8/00	7/13/00	66
GBR/008 0521	NR			
GBR/009 0512	RTC	3/20/00	5/15/00	56
GBR/009 0513	NA			
ITA/006 0506	NEL/CHR	3/14/00	8/2/00	141
ITA/006 0507	CHR	4/17/00	6/20/02	794+
ITA/011 0504	NEL	3/16/00	4/17/00	32
USA/501 0522	NR			
USA/501 0523	CHR	3/29/00	3/29/00	1+
USA/501 0524	RTC	4/26/00	4/26/00	1+
USA/501 0525	NR			
USA/501 0526	NR			
USA/501 0527	NA			
USA/502 0517	RTC	3/13/00	4/10/00	28
USA/502 0520	RTC	3/20/00	4/21/00	32
USA/502 0521	NR			
USA/502 0522	RTC	6/7/00	7/21/00	44
USA/502 0523	NR			
USA/502 0524	RTC	6/21/00	7/17/00	26+

FDA Response evaluation continued				
Country/ Center/ Subject	Best response	First day of response	Last day of response	Response duration (days)
USA/505 0514	NR			
USA/506 0509	NEL	2/14/00	5/25/00	101
USA/506 0510	NEL/CHR	2/28/00	9/14/00	199
USA/506 0526	NR			

CHR = complete hematologic response; NA = not assessable; NEL = No evidence of leukemia; NR = No response

Table 11 summarizes confirmed hematologic response rates based on sponsor analysis and **Table 12** summarizes unconfirmed hematologic response rates based on sponsor analysis .

Table 11: ALL-Hematologic Response (confirmed) - per sponsor

Initial dose	Hematologic response (confirmed)	N (%)	95 % CI	Best confirmed investigator ass.
400 mg (N=5)	Hematologic response	0		2 (40.0%)
	Complete hematologic remission	0		0
	No evidence of leukemia	0		0
	Return to chronic phase/Partial response	0		2 (40.0%)
	No response	1 (20.0%)		3 (60.0%)
	Progression	4 (80.0%)		
	Death	0		
600 mg (N=43)	Hematologic response	10 (23.3%)	11.8 - 38.6	13 (30.2%)
	Complete hematologic remission	3 (7.0%)		3 (7.0%)
	No evidence of leukemia	0		5 (11.6%)
	Return to chronic phase/Partial response	7 (16.3%)		5 (11.6%)
	No response	11 (25.6%)		26 (60.5%)
	Progression	16 (37.2%)		
	Death	2 (4.7%)		

Table 12: Hematologic Response (unconfirmed) - per sponsor

Initial dose	Hematologic response (unconfirmed)	N (%)	95 % CI	Investigator ass
400 mg (N=5)	Hematologic response	4 (80.0%)	28.4 - 99.5	4 (80.0%)
	Complete hematologic remission	0		0
	No evidence of leukemia	0		2 (40.0%)
	Return to chronic phase/Partial response	4 (80.0%)		2 (40.0%)
	No response	1 (20.0%)		1 (20.0%)
	Not assessable	0		0
	Progression	0		
	Death	0		
600 mg (N=43)	Hematologic response	24 (55.8%)	39.9 - 70.9	32 (74.4%)
	Complete hematologic remission	8 (18.6%)		11 (25.6%)
	No evidence of leukemia	3 (7.0%)		11 (25.6%)
	Return to chronic phase/Partial response	13 (30.2%)		10 (23.3%)
	No response	12 (27.9%)		10 (23.3%)
	Not assessable	1 (2.3%)		1 (2.3%)
	Progression	6 (14.0%)		
	Death	0		

Duration of hematologic response is summarized in **Table 13**.

Table 13: ALL-Duration and Time to Confirmed Hematologic Response

Initial dose		N	N Censored	Median Months	95 % CI	25th-75th Percentiles
600 mg (N=43)	Time to overall hematologic response	10	0	0.99	1.0-1.1	1.0-1.1
	Duration of overall hematologic response	10	3	3.42	2.2-6.6	2.2-6.6

Complete and partial cytogenetic responses, confirmed and unconfirmed, are listed in **Table 14.**

Table 14: Major Cytogenetic response

Country/ Center/ Subject	Best response
DEU/010 0514	CCyR (c)
DEU/010 0516	CCyR
FRA/001 0503	CCyR
FRA/001 0507	CCyR (c)
FRA/001 0508	CCyR (c)
FRA/001 0509	PCyR (c)
GBR/008 0511	CCyR (c)
GBR/008 0515	PCyR
GBR/008 0520	CCyR
ITA/006 0506	PCyR (c)
USA/502 0520	PCyR
USA/502 0522	PCyR
USA/502 0524	PCyR (c)
USA/505 0514	CCyR (c)
USA/506 0509	CCyR (c)

(c)= confirmed

Duration and time to a MCyR is listed in **Table 15**.

Table 15: Duration and Time To Cytogenetic Response

Initial dose		N	N Censored	Median months	95 % CI	25th-75th Percentiles
600 mg (N=43)	Time to MCyR	15	0	1.08	1.0-1.8	1.0-1.9
	Duration of MCyR	15	2	2.33	1.5-4.6	1.5-4.6
	Time to CCyR	9	0	0.95	1.0-2.0	1.0-2.0
	Duration of CCyR	9	2	2.20	1.0-8.4	1.6-8.4

Changes in ECOG performance status at baseline and after 3 and 6 months on study are summarized in **Table 16**. At the 400 mg/day Gleevec dose early progression was noted. This was less evident at the 600 mg/day dose.

Table 16: Performance status at baseline, 3 and 6 months

Treatment group	ECOG Score	Baseline (N= 48)	3 Months (N= 48)	6 Months (N= 48)
400 mg	Grade 0	0	1 (20.0%)	0
	Grade 1	4 (80.0%)	0	1 (20.0%)
	Grade 2	1 (20.0%)	0	0
	Grade 3	0	0	0
	Grade 4	0	0	0
	Progression	0	4 (80.0%)	4 (80.0%)
	Death	0	0	0
	Missing	0	0	0
	Total	5 (100%)	5 (100%)	5 (100%)
600 mg	Grade 0	7 (16.3%)	7 (16.3%)	4 (9.3%)
	Grade 1	15 (34.9%)	5 (11.6%)	5 (11.6%)
	Grade 2	18 (41.9%)	0	1 (2.3%)
	Grade 3	1 (2.3%)	0	0
	Grade 4	0	0	0
	Progression	0	21 (48.8%)	30 (69.8%)
	Death	0	2 (4.7%)	2 (4.7%)
	Missing	2 (4.7%)	8 (18.6%)	1 (2.3%)
	Total	43 (100%)	43 (100%)	43 (100%)

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

Gleevec treatment induced both hematologic and cytogenetic responses in this patient population of relapsed/refractory adult Ph+ ALL patients. For the 7 Ph+ ALL/LBC (lymphoid blast crisis) patients in the phase 1 study (03001) who received Gleevec doses of 600 mg/day or higher 3 had a complete hematologic response (CHR). For the 43 patients with Ph+ ALL treated with Gleevec 600 mg/day in the phase 2 study (0109) there were 3 confirmed CHR's (7%), 0 NEL (0%) and 7 RTC/PR's (16%) in the sponsor analysis. In the sponsor analysis of unconfirmed hematologic responses there were 8 CHR's (19%), 3 NEL's (7%) and 13 RTC/PR's (30%). In the FDA analysis that included both confirmed and unconfirmed responses there were 8 CHR's (19%), 5 NEL's (12%) and 11 RTC's (26%).

Major cytogenetic responses (complete or partial; confirmed or unconfirmed) were seen in 15 (30.4%) of 43 ALL phase 2 patients who received Gleevec 600 mg/day. Of the 15 patients with MCyR, 9 (60%) achieved CCyR (6 confirmed) and 6 (40%) had a PCyR (3 confirmed).

The median time to progression in study 0109 was 2.6 months (95% CI 1.9, 3.0). In the expanded access study 0114 the median TTP was 3.1 months (95% CI 3.0, 4.0).

Gleevec was generally well tolerated. The most frequently reported non-hematological AEs included nausea, vomiting, pyrexia and peripheral edema. In the population of older patients (≥ 55 years) the efficacy and safety results were comparable to those obtained in the younger population (< 55 years old).

Hematologic and cytogenetic response rates and durations were comparable in patients less than or greater than 55 years of age.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology, chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsened after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form only if the patient received study treatment. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy, when they were recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event is also be described by its duration (start and end dates), The NCI/NIH Common Toxicity Criteria version 2.0 severity grades 1 – 4, its relationship to the study drug (suspected/not suspected), and the action(s) taken.

Any Adverse Event occurring after the study completion and within four weeks of last drug intake was recorded on the Adverse Event CRF page.

Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also had to be reported to Novartis within 24-hours of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. was significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any pregnancy or fathering the child during the study will be considered as an SAE for the purpose of study reporting.

Events not considered serious are hospitalizations occurring under the following circumstances: planned before entry into the clinical study; for elective treatment of a preexisting hospitalization (unless fulfilling the criteria above); routine treatment or monitoring of the study indication and not associated with any deterioration in condition.

Any SAE occurring within four weeks after completion of the study has to be reported and recorded. In addition any pregnancy within 84 days (12 weeks, 3 months) after the last STI571 intake has to be reported and recorded as an SAE.

The institution performed laboratory analyses according to the Visit Schedules.
At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page in addition to the appropriate laboratory CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

Changes in Gleevec dose or dose interruption in patients with R/R Ph+ ALL (N=48) and lymphoid blast crisis CML (N=8) are summarized in **Table 17**.

Table 17: Dose Change or Dose Interruption

	400 mg/d N=10	600 mg/d N=46	All doses N=56
No. of patients without change of initial dose	2 (20.0)	24 (52.2)	26 (46.4)
No. of patients with change of initial dose	8 (80.0)	22 (47.8)	30 (53.6)
Change of initial dose			
Interruption (>5 days)	1 (10.0)	0	1 (1.8)
Reduction	0	7 (15.2)	7 (12.5)
Escalation	4 (40.0)	7 (15.2)	11 (19.6)
Reduction/escalation	3 (30.0)	2 (4.3)	5 (8.9)
Interruption/reduction	0	5 (10.9)	5 (8.9)
Interruption/reduction/escalation	0	1 (2.2)	1 (1.8)
Reason for dose change			
Adverse event or lab abnormality	1 (10.0)	8 (17.4)	9 (16.1)
Lack of efficacy	4 (40.0)	7 (15.2)	11 (19.6)
AE/lab abnormality/lack of efficacy	3 (30.0)	2 (4.3)	5 (8.9)
Other	0	5 (10.9)	5 (8.9)

The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported drug-related adverse events reported in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec (**Table 18**).

When imatinib was combined with high-dose chemotherapy in patients with Ph+ ALL, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed.

Table 18: AE's in PH+ ALL Patients (Study 0109)

	All grades			Grades 3 or 4		
	All ages	<55 yrs	>=55 yrs	All ages	<55 yrs	>=55 yrs
	N=56	N=38	N=18	N=56	N=38	N=18
Adverse event	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total*	56 (100)	38 (100)	18 (100)	41 (73.2)	29 (76.3)	12 (66.7)
Nausea	45 (80.4)	31 (81.6)	14 (77.8)	2 (3.6)	0	2 (11.1)
Vomiting	37 (66.1)	27 (71.1)	10 (55.6)	3 (5.4)	0	3 (16.7)
Pyrexia	22 (39.3)	14 (36.8)	8 (44.4)	4 (7.1)	3 (7.9)	1 (5.6)
Edema peripheral	21 (37.5)	12 (31.6)	9 (50.0)	2 (3.6)	2 (5.3)	0
Headache	18 (32.1)	11 (28.9)	7 (38.9)	2 (3.6)	1 (2.6)	1 (5.6)
Fatigue	17 (30.4)	10 (26.3)	7 (38.9)	0	0	0
Periorbital edema	15 (26.8)	10 (26.3)	5 (27.8)	1 (1.8)	1 (2.6)	0
Muscle cramp	14 (25.0)	10 (26.3)	4 (22.2)	1 (1.8)	1 (2.6)	0
Arthralgia	13 (23.2)	8 (21.1)	5 (27.8)	0	0	0
Cough	13 (23.2)	9 (23.7)	4 (22.2)	0	0	0
Abdominal pain upper	12 (21.4)	7 (18.4)	5 (27.8)	0	0	0
Diarrhea	12 (21.4)	7 (18.4)	5 (27.8)	1 (1.8)	1 (2.6)	0
Constipation	11 (19.6)	7 (18.4)	4 (22.2)	0	0	0
Neoplasm malignant	11 (19.6)	5 (13.2)	6 (33.3)	7 (12.5)	5 (13.2)	2 (11.1)
Pain in extremity	11 (19.6)	9 (23.7)	2 (11.1)	1 (1.8)	0	1 (5.6)
Asthenia	10 (17.9)	7 (18.4)	3 (16.7)	0	0	0
Bone pain	10 (17.9)	7 (18.4)	3 (16.7)	1 (1.8)	1 (2.6)	0
Dyspnea	8 (14.3)	6 (15.8)	2 (11.1)	4 (7.1)	3 (7.9)	1 (5.6)
Hypokalemia	8 (14.3)	5 (13.2)	3 (16.7)	0	0	0
Night sweats	8 (14.3)	6 (15.8)	2 (11.1)	1 (1.8)	1 (2.6)	0
Abdominal pain	7 (12.5)	5 (13.2)	2 (11.1)	0	0	0
Anorexia	7 (12.5)	4 (10.5)	3 (16.7)	1 (1.8)	1 (2.6)	0
Dizziness	7 (12.5)	5 (13.2)	2 (11.1)	0	0	0
Nasopharyngitis	7 (12.5)	5 (13.2)	2 (11.1)	0	0	0
Abdominal discomfort	6 (10.7)	2 (5.3)	4 (22.2)	0	0	0
Back pain	6 (10.7)	2 (5.3)	4 (22.2)	1 (1.8)	0	1 (5.6)
Hematoma	6 (10.7)	2 (5.3)	4 (22.2)	0	0	0
Insomnia	6 (10.7)	3 (7.9)	3 (16.7)	0	0	0
Myalgia	6 (10.7)	5 (13.2)	1 (5.6)	1 (1.8)	0	1 (5.6)

Hematologic Toxicity

Cytopenias, particularly neutropenia and thrombocytopenia, were a consistent finding in all Gleevec studies, with a higher frequency at doses ≥750mg/day (Phase 1 study).

Cytopenias 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% of treated patients and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of CML patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and grade 3 or 4 SGOT (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in 2.7% of patients.

When imatinib was combined with high dose chemotherapy regimens in patients with Ph+ ALL, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed. Monitoring of liver function should be considered in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.

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 other 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.

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, acute febrile neutrophilic dermatosis (Sweet's syndrome)

Digestive: *Less common*: abdominal distention, gastroesophageal reflux, mouth ulceration
Infrequent: gastric ulcer, gastroenteritis, gastritis
Rare: colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor necrosis, gastrointestinal perforation
General Disorders and Administration Site Conditions: *Rare*: tumor necrosis
Hematologic: *Infrequent*: pancytopenia
Rare: aplastic anemia
Hepatobiliary: *Uncommon*: hepatitis
Rare: hepatic failure
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
Rare: avascular necrosis/hip osteonecrosis
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

7.1.1 Deaths

Table 19 indicates deaths on study or within 28 days of completion. All patients died of progression or complications related of the underlying disease.

Table 19: Deaths- Study 0109

	400 mg N=10	600 mg N=46	All doses N=56
Deaths	**n (%)**	**n (%)**	**n (%)**
Total number of deaths	10 (100)	42 (91)	52 (93)
Deaths during study	1 (10.0)	3 (6.5)	4 (7.1)
Deaths within 28 days of last dose of study drug	2 (20.0)	11 (23.9)	13 (23.2)
Deaths after 28 days of last dose of study drug	7 (70.0)	28 (61)	35 (62.5)

7.1.2 Other Serious Adverse Events

None

7.1.3 Dropouts and Other Significant Adverse Events

Two patients discontinued therapy; Patient 101/182 had grade 2 increased AST/ALT on day 184. Patient 501/115 had grade 2 Nausea/Vomiting on day 2.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

See Table 18

7.1.6 Laboratory Findings

See Table

7.1.7 Vital Signs

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

7.1.8 Electrocardiograms (ECGs)

No ECGs were performed for study 0109.

7.1.9 Immunogenicity

There is no new relevant information.

7.1.10 Human Carcinogenicity

There is no new relevant information.

7.1.11 Special Safety Studies

There is no new relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Gleevec has no known potential for abuse..

7.1.13 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
- PSUR 7 covering the period 11 May 2005 - 10 May 2006
- 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 "Sweet's Syndrome" was proposed for inclusion to the BPI.

In 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 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.

In PSUR 7 and in a recent literature report congestive heart failure and left ventricular dysfunction associated with Gleevec treatment were updated. A recent article published online in Nature Medicine (Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine; advance online publication July 23rd. 2006) reported 10 Gleevec treated patients who developed severe congestive heart failure and left ventricular dysfunction. Supplemental data available on the Nature Medicine website show that prior to Gleevec treatment all 10 patients had New York Heart functional class 1 and normal left ventricular ejection fractions. Some of these patients had pre-existing conditions including hypertension, diabetes and coronary artery disease. In an abstract published in the Journal of Cardiac Failure (Iliescu C, Wamique Yusuf S, Auerbach L, et al. Impact of angiotensin converting enzyme inhibitors & carvedilol on recovery of cardiac function in imatinib associated cardiomyopathy. Journal of Cardiac Failure 2005; 40 No. 6 Suppl. Abstract 054. 9th Annual Scientific Meeting of the Heart Failure Society of America, Sept 18-21st 2005) the authors stated that treatment with angiotensin converting enzyme inhibitors (ACE-I) and carvedilol resulted in significant improvements in left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) Class. Three of these patients, when re-challenged, were reported to have no further diminution of cardiac function.

The Nature Medicine article also reports on preclinical studies showing that Gleevec treated mice develop left ventricular contractile dysfunction. Gleevec also induces cell death in isolated cardiomyocytes. The authors hypothesize that development of cardiac dysfunction is related to inhibition of the Abl receptor and may be a possibility with any drug that targets the Abl receptor.

A thorough review of the sponsor's safety database yielded 148 spontaneous cases of cardiac events. The median age was 65 years. Of 117 patients with sufficient clinical information for analysis approximately 50% had a history of cardiovascular disease before the onset of Gleevec treatment (mostly hypertension and ischemic heart disease), 40% were on cardiac medications and 8.5% experienced worsening of preexisting heart disease.

Thus heart failure is a recognized, potentially severe, but uncommon complication of Gleevec therapy. Current information does not support routine screening and monitoring of cardiac function in patients taking Gleevec. Any patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with symptoms consistent with cardiac failure should be aggressively evaluated and treated.

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

The duration of exposure of study 0109 patients is described in **Table 20.** This duration of exposure is likely that which would be expected in an advanced relapsed/refractory ALL patient population.

Table 20: Duration of exposure (study 0109)

	400 mg/d N=10	600 mg/d N=46	All doses N=56
Duration of exposure (days)			
n	10	46	56
mean	82.6	143.2	132.3
s.d.	72.44	244.37	224.20
median	51.0	63.0	62.0
25-75th percentiles	46-71	36-126	41-119
minimum -maximum	32-264	14-1356	14-1356
Duration of exposure			
< 3 months	8 (80.0)	30 (65.2)	38 (67.9)
>= 3 months - < 6 months	1 (10.0)	8 (17.4)	9 (16.1)
>= 6 months - < 12 months	1 (10.0)	5 (10.9)	6 (10.7)
>= 12 months - < 24 months	0	1 (2.2)	1 (1.8)
>= 24 months - < 36 months	0	1 (2.2)	1 (1.8)
>= 36 months	0	1 (2.2)	1 (1.8)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Prior Gleevec reviews of CML chronic phase, accelerated phase and blast crisis and of GIST.

7.2.3 Adequacy of Overall Clinical Experience

AE's associated with Gleevec treatment have been well described.

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 drug related AEs occurred in 2%, of patients in chronic phase CML. 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 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 was associated with grade 3/4 neutropenia 12% of patients and grade 3/4 thrombocytopenia in 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 currently reported AE's in patients with Ph+ ALL are similar to the above known Gleevec adverse effects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Separate safety data has been provided for each Gleevec indication. Because of different Gleevec doses for solid tumors and hematologic malignancies, because of the relatively small number of Ph+ ALL patients studied and because of the large amount of safety data already available it was not felt to be worthwhile to pool safety data. .

7.4.2 Explorations for Predictive Factors

Predictive factors including dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions were not explored in the current study.

7.4.3 Causality Determination

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

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. The recommended doses of 600 mg for patients with Ph+ ALL has been based on the findings of the initial phase I trial 03 001, subsequently confirmed by the phase II trial 0109.

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 information is available.

8.5 Advisory Committee Meeting

An ODAC meeting to discuss this application is not planned.

8.6 Literature Review

Thomas DA, Fardel S, Cortes J et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood 103 (12): 4396-4407

Thomas DA et al. Update of the hyper-CVAD and the imatinib mesylate regimen in Philadelphia-positive acute lymphoblastic leukemia (ALL). ASH Annual meeting 2004; 104 (11): abstract 2738.

Lickliter J, Arthur C, D'Rosario J (2004) Phase II Pilot Study of Imatinib Mesylate Combined with Induction Chemotherapy in Blast CML and Ph+ ALL. ASH Annual meeting 2004; 104 (11): abstract 4682.

Lickliter J et al. (2005) Phase II Pilot Study of Imatinib Mesylate Combined with Induction Chemotherapy in Philadelphia chromosome-positive acute leukemias. Manuscript submitted

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 OVERALL ASSESSMENT

9.1 Conclusions

The reviewer concurs with the sponsor's assessment of efficacy and safety of Gleevec monotherapy for the treatment of adult patients with relapsed or refractory Ph+ ALL. patients.

The sponsor's conclusions were:

b(4)

- An initial dose of 400 mg is not effective [redacted]. Treatment with an initial dose of 600 mg daily

produced sustained hematologic responses in 12 (26.1%) patients. Four (33%) of them achieved sustained CHR.

- The median time to hematologic response was 1 month in the whole patient population. However, as a single agent the median duration of hematologic response was short at 3.42 months in the whole population and 4.67 months in older patients (≥ 55 years old).
- Confirmed major cytogenetic responses were seen in 12 (26.1%) patients treated with 600 mg . Seven (58%) of them achieved a complete cytogenetic response .
- The median time to progression in patients started with 600 mg was 2.56 months and 2.79 months in older patients. Median survival was 4.99 months in the whole population compared to 7.43 months in older patients (≥ 55 years old).
- In general the study drug was well tolerated and premature discontinuation of therapy due to AEs were rare. Instead, ten of the 11 patients who discontinued therapy due to AEs discontinued due to progression of the underlying disease, and one case was due to neutropenia associated with pneumonia
- The most frequently reported non-hematological AEs included nausea, vomiting, pyrexia and peripheral edema. The results suggest that STI571 600 mg daily used as a single agent represents an effective therapeutic agent for the salvage treatment of patients with relapsed/refractory Ph+ALL. In the population of older patients (≥ 55 years) the results were comparable to those obtained in the younger population (< 55 years old). STI571 600 mg daily was also demonstrated to be safe and well tolerated in the population of relapsed/refractory Ph+ALL including in the elderly patients.

9.2 Recommendation on Regulatory Action

The proposed indication is: "Gleevec is indicated as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL".

The clinical reviewer recommends that Gleevec receive regular approval for this indication. This is based upon the induction of both hematologic and cytogenetic responses in this patient population. For the 7 Ph+ ALL/LBC patients in the phase 1 study (03001) who received Gleevec doses of 600 mg/day or higher 3 had a complete hematologic response (CHR). For the 43 patients with Ph+ ALL treated with Gleevec 600 mg/day in the phase 2 study (0109) there were 3 confirmed CHR's (7%), 0 NEL (no evident leukemia) and 7 RTC/PR's (16%) in the sponsor analysis. In the sponsor analysis of unconfirmed hematologic responses there were 8 CHR's (19%), 3 NEL's (7%) and 13 RTC/PR's (30%). In the FDA analysis that included both confirmed and unconfirmed responses there were 8 CHR's (19%), 5 NEL's (12%) and 11 RTC's (26%).

Major cytogenetic responses (complete or partial; confirmed or unconfirmed) were seen in 15 (35%) of 43 Ph+ ALL phase 2 patients who received Gleevec 600 mg/day. Of the 15 patients with MCyR, 9 (21%) achieved CCyR (6 confirmed) and 6 (14%) had a PCyR (3 confirmed).

The Gleevec team is reviewing 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 phase 4 commitments.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Label is being reviewed by DODP Gleevec team.

9.5 Comments To Applicant

None.

10.0 APPENDICES

10.1. Review Of Individual Study Reports

Study AUS01 - MD Anderson Cancer Center

A Phase II study of hyper-CVAD plus STI571 for Philadelphia-positive acute lymphoblastic leukemia. The primary study nobjective was to determine the clinical efficacy (overall response rate, event-free survival, and survival) and safety of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with STI571 for Ph+ ALL). Forty patients were to be enrolled. Therapy included eight induction-consolidation courses alternating hyper-CVAD with high dose methotrexate (MTX) and cytarabine (ara-C), concurrently with imatinib. STI-571 400 mg po daily was given days 1 to 14 of each course of intensive chemotherapy)

From April 2001 to February 2004, 32 patients have been enrolled in this study out of the 40 patients planned with a median age of 48 years (range, 17-75 years). Twenty-six patients had active disease, either untreated or refractory to one induction course without imatinib. Six patients were in CR at study entry after one induction course without imatinib. Twenty-five (96%) out of the 26 patients with active disease achieved complete response (one failed to meet platelet criteria for CR). At the time of the analysis the median follow-up was 24 months (range, 4-36 months). The outcome appears to be better with the hyper-CVAD chemotherapy combined with imatinib with 2-year DFS rates of 87% (for all patients) compared to the historical controls, 28% for hyper-CVAD alone and 12% for VAD ($p<0.001$).

Five patients died (3 older patients related to comorbidity, and 2 due to complications of allogeneic stem cell transplantation). No patient discontinued therapy with imatinib. In the first 20 patients treated, the median time to hematologic recovery was not significantly different from the prior non-imatinib regimens. The median time to neutrophil recovery to ANC of 109/L or higher ranged from 12 to 28 days (during the induction course). The median time to recovery of the platelet count to 50 x 109/L or higher ranged from 14 to 21 days (during the induction course).

The author's preliminary conclusions was that the outcome of the hyper CVAD (cyclophosphamide, vincristine Adriamycin, and dexamethasone), a dose-intensive chemotherapy regimen and imatinib mesylate for patients with de novo Ph-positive ALL appears significantly better than the conventional chemotherapy programs such as VAD or CVAD without imatinib.

Study AAU02 - 11 centers in Australia- ALLG study group

Study AAU02 is titled "A phase II pilot study of Gleevec (imatinib mesylate, STI571) combined with induction chemotherapy in blast-phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia." The primary objective is to determine the safety and tolerability of Gleevec at 600 mg daily in combination with induction chemotherapy in adult patients with CML in blast crisis or Ph+ ALL.

In CML-LBC and in relapsed Ph+ALL imatinib was administered as follow: 600 mg up front for 7 days then combined with induction chemotherapy until day 7 and then withheld until blood count recovery (neutrophils > 1.0 x 109/L and platelets > 20 x 109/L) and recommenced at 600 mg daily and continued until the occurrence of disease progression, relapse, excessive toxicity or withdrawn from the study. The duration of Gleevec therapy will be for a core period of 12 months, with possible extension for a further 12 to 24 months. In de novo Ph+ALL: Imatinib was administered prior to induction therapy only. For patients with de-novo Ph+ ALL chemotherapy will be given according to the French cooperative group ALL protocol (LALA 94).

Among 22 evaluable patients, combined imatinib and chemotherapy induction resulted in 14 (64%) complete hematological response. There were 7 (58%) complete hematological responses among 12 evaluable patients with de-novo Ph+ ALL and 7(88%) CR among 8 evaluable relapsed Ph+ALL and CML-LBC. Complete cytogenetic response were seen in 9 (45%) among 20 evaluable patients. Neutrophils recovered to $\geq$ 1.0 x 109/L at a median of day 24 of induction chemotherapy, with only 1 patient showing delayed recovery (> day 42). There was 1 induction death on day 18 from overwhelming sepsis and multi-organ failure. No unexpected non-hematological toxicities were observed. The in-vivo inhibition of Bcr-Abl by imatinib was monitored in leukemic cells during the imatinib-only prephase using Western blot analysis of CrkL phosphorylation status. Marked dephosphorylation of CrkL was observed in peripheral blood and/or marrow in all but 1 of 8 evaluable cases. Imatinib potently inhibited Bcr-Abl activity in vivo in Ph+ acute leukemic blasts and its

combination with induction chemotherapy was tolerable. This strategy deserves further study.

Neutrophils recovered to ≥ 1.0 x 109/L at a median of day 24 of induction chemotherapy, with only 1 patient showing delayed recovery (> day 42). There was 1 induction death on day 18 from overwhelming sepsis and multi-organ failure. No unexpected non-hematological toxicities were observed.

In conclusion, Imatinib potently inhibited Bcr-Abl activity in vivo in Ph+ acute leukemic blasts and its combination with induction chemotherapy was tolerable.

10.2 Line-By-Line Labeling Review

Done.

10.3 DSI Inspection

The following are "preliminary results" from NEW-DO and from NYK-DO regarding the inspections of Dr. George Demetri and Dr. Richard Silver for NDA-21588/S-011 and S-013 for Gleevec®. Based on no FDA 483s issued, both sites appear to be in compliance with the applicable GCP regulations.

NWE-DO
Dr. George Demetri (Study B2225) (Site 501) (6 subjects)
DFCI & Harvard Medical School
Inspection completed on April 28, 2006.
No FDA 483 was issued. At lease two instances of minor deviations from the protocol related to the +/-2 day visit window(4 out of 6 subjects had visits outside this 2 day window) and subjects being provided much larger quantities of study medications (up to 6 month supplies were given to some subjects; the protocol required up to 6 weeks supply). However, these deviations were discussed and approved by the sponsor.

NYK-DO
Dr. Richard T. Silver (Study B2225) (Site 506) (5 subjects)
New York Hospital- Cornell
Inspection completed April 26, 2006
No FDA 483 was issued. Study records and documentations at this site were found to be highly organized; studies were meticulously monitored by the regulatory staff of Cornell and under the close supervision of the sponsor. Data listings and the reporting of AEs and SAEs were found to be accurately reported. Drug accountability records were in good order.

I would like to forward the following additional observations made by the FDA Field Investigator related to bone marrow cytogenetic study requirement (to be done at screening and weeks, 13 and 25 per protocol). I wanted to see if you have any further issues or

comments with regard to cytogenetic screening/cytogenetic response or Dr. Silver's comments about FDA requirements with regard to the following five subjects at this site:

Subject 502 ——
Review of the bone marrow analysis CRF respectively for week five dated 24 November 1999 and week nine dated 23 December 99 revealed that the bone marrow cytogenetic analysis was not done. This deviation was attributed to a dry tap during the biopsy. This observation was discussed with Dr. Silver during the inspection and at the close out discussion. However upon review of the protocol bone marrow cytogenetic studies schedule this requirement was to be done at screening and weeks, 13 and 25. There was no protocol violations listed for this subject as part of the NDA listing. b(6)

Subject 509 ——
The subject entered the study on 1/13/2000. The screening cytogenetic report dated 1/12/00 based on a specimen date of 1/6/00 reads in part, "A bone marrow sample received on 1/6/00 was clotted on arrival. Unstimulated 24-hour cultures were set up as per protocol. The cultures failed to grow." Review of the subjects medical record revealed that there was adequate documentation to support the diagnosis of the Philadelphia chromosome positive ALL. A cytogenetics report dated 5/16/00 with a specimen date of 2/14/00 utilizing fluorescent in situ hybridization (FISH) with the BCR/ABL DNA probe revealed 12.5% Ph positive and 87.5% Ph negative interfaces were found. The protocol violation section of the NDA states that subject 509 be excluded per protocol analysis (cytogenetic response) as the protocol violation reads, "Ph chromosome negative at baseline." b(6)

Subject 510 ——
The subject entered the study on 1/21/2000.
The screening cytogenetics report date 1/28/00 based on a specimen date of 1/19/00 was negative for Philadelphia positive chromosome. However, review of the medical records revealed that there was adequate documentation to indicate that the subject was clinically positive for Ph positive ALL. The protocol violation section of the NDA states that subject 510 be excluded from per protocol analysis (cytogenetic response). b(6)

Subject 526 ——
Subject entered the study on 2/17/00. The bone marrow specimen was obtained on 2/16/00. The screening bone marrow cytogenetic analysis was not done because of a dry tap bone marrow aspirate. The bone marrow specimen was only enough to be sent for surgical pathology and not cytogenetics. The molecular pathology report date 2/15/00 based on a specimen date of 2/4/00 indicates BCR-ABL analysis consistent with a presence of a Philadelphia chromosome (t 9; 22). In addition, the cytogenetics report dated 1/13/00 based on a specimen date of 11/30/99 indicates that the Philadelphia chromosome was present in 100% of the cells studied. Lastly various components of the blood chemistry for the week one day one visit was not done. b(6)

The protocol violation section of the NDA states that subject 506 has minor protocol violations as there is no documentation of Ph chromosome positivity (Ph missing at baseline).

Subject 520 ____ b(6)

Review of the bone marrow analysis CRF respectively for week five dated 13 March 2000 revealed that the bone marrow cytogenetic analysis was not done. This observation was discussed with Dr. Silver during the close out discussion. This deviation was attributed to a dry tap during the biopsy However upon review of the protocol bone marrow cytogenetic studies schedule required this to be done at screening and weeks, 13 and 25. The blood chemistry week one day one visit two was not done as part of day one of dosage. There was no protocol violations listed for this subject as part of the NDA listing

These aforementioned observations were discussed with the regulatory coordinators during the conduct of the inspection and with Dr. Silver as noted. A close out discussion was conducted with Dr. Silver and the regulatory coordinators. No FDA 483 was issued. Dr. Silver acknowledged the inspectional findings and made comments with regard to the definitive diagnosis of Philadelphia positive chromosome as it pertains to the bone marrow cytogenetic studies and fluorescent in situ hybridization (FISH) using the BCR/ABL DNA probe. He stated that he made it very clear during the investigator meetings that they were not doing the BCR/ABL test or FISH analysis. He stated that because of this there would be deficiencies noted and he has written various articles in the literature about this. He stated that Novartis was made aware of this. However FDA considered the bone marrow cytogenetic studies as the standard. During discussions with Novartis, he made them aware that utilizing traditional bone marrow biopsies could result in dry taps because of a lack of aspirate and recommended that BCR/ABL test be used as there is a question of sensitivity utilizing bone marrow cytogenetic testing. Dr. Silver requested that I include this information as part of my report. Dr. Silver will respond to any correspondence received by FDA.

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9/8/2006 10:07:12 AM
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Application Type	NDA 21-588
Submission Number	SE1
Submission Code	014 (Systemic Mastocytosis)
Letter Date	2/28/06
Stamp Date	2/28/06
Reviewer Name	Martin H. Cohen, M.D.
Statistician	Kun He, 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	S

Formulation

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

Dosing Regimen

In patients with hematologic malignancies, including systemic mastocytosis (SM), in Study B2225 imatinib therapy was initiated at a dose level of 400 mg/day.

In the published literature SM patients received doses ranging from 100 mg to 400 mg daily. The small number of patients involved makes it impossible to do a dose/efficacy comparison and no dose finding studies have been performed. From the reports, the dose selection used was likely a mixture of influences including the known literature existing for the treatment of hypereosinophilic syndrome (HES) where doses of 100-400 mg/day have been employed, the known tendency of SM patients to have various hematologic disorders associated with eosinophilia, the recognition of FIP1L1 mutation sensitivity to imatinib, and the clinical situation of the patients. The largest clinical experience comes from the Mayo Clinic where several of their patients were started on imatinib at 400 mg/day and then reduced to 100 mg/day following improvement; other patients were started at 100 mg/day and then escalated to 400 mg/day if no improvement was seen.

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(s)

Proposed Indication: Gleevec is indicated for the treatment adult patients with systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown.

Other Indications: 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

The approved indication should be for the treatment adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown". Approval does not include patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

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1.0 EXECUTIVE SUMMARY

Gleevec should be granted regular approval for the following indication: "Gleevec is indicated for the treatment adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown". Approval does not include patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec".

One uncontrolled study (B2225) enrolling 5 patients and ten publications including 25 SM patients (23 aggressive SM) support the efficacy claim. Eight out of the 28 patients with aggressive SM (30%) experienced a complete hematological response. In Study B2225 one patient had a confirmed partial response, a second patient had an unconfirmed partial response, and one further patient experienced stable disease as best overall response. In the published literature, eight patients experienced a partial response. Overall, counting confirmed complete and partial responders, imatinib induced a hematological response in 17 out of 28 patients (61%). In addition to improvement in hematologic and bone marrow abnormalities there were also improvements in symptomatology and other organ dysfunction abnormalities.

Cytogenetic abnormalities were evaluated in 20 of the 23 patients with aggressive SM treated in the published reports. Seven out of these 20 patients had FIP1L1-PDGFRα fusion kinase, as determined either by actual mutational analysis showing FIP1L1-PDGFRα fusion kinase or by a CHIC2 allele deletion detected by FISH methodology implying presence of the FIP1L1-PDGFRα fusion kinase. Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their SMCD. Two patients showed a c-Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I). Patients that harbor the D816V mutation of c-Kit are not sensitive to imatinib. All 7 patients with the FIP1L1-PDGFRα fusion kinase had a CHR.

Recommendation On Regulatory Action

The medical reviewer recommends that regular approval be granted for the following indication:. "Gleevec is indicated for the treatment adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown". Approval does not include patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

Clinical benefit is demonstrated by long duration responses. Further, the rarity of occurrence of aggressive SM with absent c-Kit D816V mutation makes randomized trials

impractical. The number of patients suffering from smoldering and aggressive SM in the USA is estimated to be 20,000, among which 8,000 are adults and 12,000 children. Kit D816V mutation is present in approximately 60% of the adults, leaving 3000 adults without D816V mutation. Aggressive mastocytosis represents less than 5% of adult cases or less than 150 patients.

A summary of responses in aggressive SM is shown below.

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	7	7 (100%)	0
Juxtamembrane mutation	2	0	2 (100%)
Unknown or no cytogenetic abnormality detected	15	0	7 (44%)
D816V mutation	4	1* (25%)	0
Total	28	8 (30%)	9 (32%)
*Patient had concomitant CML and SM			

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 commitments.

1.23 Other Phase 4 Requests

Assure availability of a validated test kit for detection of the D816V c-kit mutation. An IDE or Pre-Market Application filing by Novartis or a 3rd party should occur no later than 4 months after Gleevec approval for this indication.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

One open-label, multicenter, Phase II clinical trial (study B2225) was conducted. This study included 5 patients with SM. The SM patients were treated with 100 mg to 400 mg of Gleevec daily. In addition to these 5 patients, 10 published case reports and case series describe the use of Gleevec in 25 additional patients with SM aged 26 to 85 years. These 25 patients also received 100 mg to 400 mg of Gleevec daily (**Table 1**).

Table 1: SM - Literature Reports

Study	No. of patients treated with imatinib	Potential genotypic mutations	Dose of imatinib (mg/day)	Study design description
Pardanani, et al (2003a)	12	c-Kit activating	100 – 400	Case Series
Pardanani, et al (2003b)	5 patients, all reported in Pardanani, et al (2003a)	FIP1L1-PDGFRα, c-Kit activating	100 – 400	Case Series
Pottier, et al (2003)	1	Not described	400	Case Report
Akin, et al (2004)	1	Phe522Cys	400	Case Report
Elliott, et al (2004)	1	FIP1L1-PDGFRα	100 – 400	Case Report
Hennessy, et al (2004)	3 (out of 18 patients in total)	Not sought	200 – 400	Case Series
Musto, et al (2004)	1	D816V	400	Case Report
Pardanani, et al (2004a)	7 patients,3 already reported in Pardanani, et al (2003a)	FIP1L1-PDGFRα	100	Case Series
Agis, et al (2005)	1	D816V	400	Case Report
Zhang, et al (2005)	1	K509I	400	Case Report
Total	25			

1.3.2 Efficacy

One uncontrolled study (B2225) enrolling 5 patients and ten publications including 25 SM patients (23 aggressive SM) support the efficacy claim. Eight out of the 28 patients with aggressive SM (30%) experienced a complete hematological response. In Study B2225 one patient had a confirmed partial response, a second patient had an unconfirmed partial response, and one further patient experienced stable disease as best overall response. In the published literature, eight patients experienced a partial response. Overall, counting confirmed complete and partial responders, imatinib induced a hematological response in 17 out of 28 patients (61%). In addition to improvement in hematologic and bone marrow abnormalities there were also improvements in symptomatology and other organ dysfunction abnormalities.

Cytogenetic abnormalities were evaluated in 20 of the 23 patients with aggressive SM treated in the published reports. Seven out of these 20 patients had FIP1L1-PDGFRα fusion kinase, as determined either by actual mutational analysis showing FIP1L1-PDGFRα fusion kinase or by a CHIC2 allele deletion detected by FISH methodology implying presence of the FIP1L1-PDGFRα fusion kinase. Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their SMCD. Two patients showed a c-Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I). Patients that harbor the D816V mutation of c-Kit are not sensitive to imatinib. All 7 patients with the FIP1L1-PDGFRα fusion kinase had a CHR.

A summary of the response rates to Gleevec in SM is provided in **Table 2**.

Table 2: Response in Aggressive SM by cytogenetics

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	7	7	0
Juxtamembrane mutation	2	0	2
Unknown or no cytogenetic abnormality detected	15	0	7
D816V mutation	4	1*	0
Overall totals	28	8 (30%)	9 (32%)
*Patient had concomitant CML and SM			

1.3.3 Safety

Adverse events in SM patients were similar to those observed in other Gleevec studies. Most were of CTC grade 1 or 2 in severity. AE's included nausea, diarrhea, fatigue, muscle cramps, arthralgia and fluid retention. Laboratory abnormalities included anemia.

SM might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should be therefore considered in those SM patients. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should therefore be considered at the initiation of therapy.

Follow-up, to-date indicate that the following toxicities may be of concern:

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome. In some reported cases a recurrent dermatologic reaction was observed upon rechallenge. Several 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. 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. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST. There have been post-marketing reports, including fatalities, of

cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with Gleevec.

Gastrointestinal Disorders: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

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. 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. In patients with hypereosinophilic syndrome and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in SM patients associated with high eosinophil levels. If either is abnormal, prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Gleevec.

Toxicities From Long-Term Use: Potential toxicities suggested by animal studies, include 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).

1.3.4 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 100mg/day to 400 mg/day for adult patients with SM.

1.3.5 Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: 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.

CYP3A4 Substrates: 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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (**Table 3**) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 3: Liver Function Classification

Test	Normal (n=14)	Mild (n=30)	Moderate n=20	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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.

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 Abl tyrosine kinase at the in vitro, cellular, and in vivo level. The compound specifically inhibited proliferation of v-Abl and Bcr-Abl expressing cells, suggesting that it is not a general antimitotic agent. In colony formation assays using progenitor cells ex vivo from patients with CML, imatinib showed selective inhibition of Bcr-Abl positive colonies. In addition, imatinib potently inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ), c-Kit, the receptor for stem cell factor (SCF), c-Fms, the receptor for macrophage stimulating factor (M-CSF), as well as Abl and Arg PTK. Imatinib also inhibits the cell signaling events mediated by activation of Bcr-Abl, c-Kit and the PDGF receptors. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor, insulin and phorbol esters. In vivo, the compound shows anti-tumor activity as a single agent in animal models at well tolerated doses.

2.2 Currently Available Treatment For Proposed Indication

Therapy for mast cell disorders is aimed at both symptomatic care and the control of mast cell burdens within the body. Symptomatic control of episodes of cytokine release relies on the antihistamines (both H1 and H2 receptor blockade), epinephrine, and the avoidance of precipitating factors. Topical steroids and psoralen plus ultraviolet A light exposures (PUVA therapy) have been used for topical disease. Oral disodium cromoglycolate can reduce pruritis and wheal formation in the skin. Diphosphonates are used to control osteopenia. For patients with aggressive SM and rapidly progressive splenomegaly, splenectomy has been performed with clinical benefit observed. In patients with mast cell leukemias or SM associated myeloproliferative disorders, interferon and cytotoxic chemotherapy regimens have been employed.

2.3 Availability Of Proposed Active Ingredient In The United States

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

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

The clinical results were discussed with the FDA on 12-Aug-2004. The objective of this meeting was to seek guidance for the approval of imatinib as a treatment for patients with rare malignancies carrying imatinib-sensitive targets. The FDA recognized the rarity of the targeted malignancies and accepted to consider a potential filing based upon an exploratory phase II study and published case reports/studies. Suggestions and recommendations on how to analyze and present the data were also given.

2.6 Other Relevant Background Information

Systemic mastocytosis is a clonal expansion of mast cells. Mast cells are derived from CD34+ pluripotential stem cells that are marrow derived and then migrate to peripheral tissues for terminal differentiation. Cutaneous mastocytosis (CM) is characterized by cutaneous infiltrations of mast cells that cause local inflammatory and fibrosing reactions. These can develop at a very young age and be either localized or more extensive. When mast cells are recognized to be infiltrating multiple organs, then the term systemic mastocytosis (SM) is generally clinically applied. Certain patients with SM also exhibit an associated myeloproliferative or myelodysplastic disorder in the bone marrow. The development of these conditions in association with mast cell disorders has been taken as evidence of the clonal derivation of mast cells from myeloid precursors. In these instances the prognosis is generally determined by the associated disorder. The World Health Organization (WHO) criteria for the diagnosis of SM are as follows **(Table 4)**: Diagnosis requires one major and one minor criterion or three minor criteria.

Table 4: WHO criteria for a diagnosis of SM: Major Criterion* Minor Criteria*

Major Criterion*	Minor Criteria*
Multifocal dense infiltrates of mast cells (15 or more mast cells in aggregates) in biopsy sections of the bone marrow and/or other extracutaneous organ or organs, confirmed by special stains such as mast cell tryptase	In sections of bone marrow or other extracutaneous organs, more than 25% of mast cells are spindle-shaped or otherwise atypical or, in a bone marrow aspirate, more than 25% of mast cells are typical or immature; Kit codon 816 mutation is present in extracutaneous tissues Extracutaneous mast cells co-express CD117 and either CD2, CD25, or both; Serum tryptase is persistently greater than 20 mg/mL (unless there is an associated clonal myeloid disorder, in which case this criterion is not valid)

Additional search for organ infiltration is made with liver/spleen scans, CT scans searching for organ infiltration/enlargement and lymph node enlargement, and gastrointestinal evaluations as indicated for gastrointestinal complaints. Marrow infiltration leads to anemia, other cytopenias, and skeletal abnormalities including osteopenia. Splenomegaly may contribute to the cytopenias and patients may have superficial or internal lymphadenopathy. Clinically, patients may also describe episodes of generalized flushing or "warm feelings" accompanied by shortness of breath, palpitations, tachycardia, nausea, diarrhea, lightheadedness, headache, and occasionally hypotension and syncope. Following the episodes the patients may experience fatigue lasting several hours. Precipitating events for these attacks may include stress, exertion, or heat exposure.

The role of genetics in SM

Disorders of mast cells and their response to therapy are now being molecularly defined. Mast cells terminally differentiate in the peripheral tissues under the control of c-Kit and its ligand, SCF, in addition to other cytokines. SCF is primarily produced by tissue stromal cells. Abnormalities of regulation of the c-Kit/SCF axis may lead to dysregulation of mast cell proliferation in tissues. The focal accumulation of dermal mast cells has been associated with increased amounts of SCF in tissues. Not all patients with

SM have identifiable activating mutations of c-Kit and these patients may have abnormalities in the regulation of the c-Kit/SCF axis or other yet undiscovered pathogenetic disorders. Mutations of c-Kit codons 560 and 816 that lead to ligand-independent c-Kit kinase activation have been described in human mast cell leukemia lines. The D816V mutation is the most common mutation found and may be most prevalent in the indolent form of SM. The D816V Kit activating mutation is located within the activation loop of the kinase domain and confers resistance to imatinib by virtue of a structural change leading to a destabilization of the inactive conformation of the kinase. Both in vitro cell lines and patient derived mast cells that harbor the D816V mutation of c-Kit are not sensitive to imatinib. Although a single case report published by Agis, et al (2005) indicated sensitivity to imatinib therapy in a patient with SM and the D816V mutation (this patient had concomitant Ph+ CML), the larger body of clinical evidence does not support the effectiveness of imatinib therapy in the treatment of patients with SM who have the D816V mutation. Other mutations, such as the V560G juxtamembrane mutation of c-Kit are sensitive to imatinib in vitro, and patients harboring this mutation have also derived clinical benefit from imatinib therapy. Activating mutations involving the juxtamembranous codons interfere with the "control" function of the tyrosine kinase, but remain sensitive to imatinib inhibition. Patients with SM and wild type c-Kit have also been described to benefit from imatinib therapy. In a subset of SM patients with associated eosinophilia, a novel tyrosine kinase generated from the fusion of the Fip1-like-1 (FIP1L1) gene with the PDGFRα gene has been described by Pardanani, et al (2003b). The fusion results from an interstitial deletion that includes the CHIC2 locus on chromosome 4q12. The FIP1L1-PDGFRα is a constitutively activated PTK that is highly sensitive to imatinib. Patients with SM with associated eosinophilia and FIP1L1-PDGFRα are often male and develop rapid and complete response to treatment with imatinib.

The increased understanding of the role of genetics in the etiology of SM has added to the clinicopathologic classifications of patients with mast cell disorders. **Table 4** above incorporates c-Kit mutation information into the diagnostic criteria for SM and **Table 5** below is the latest consensus classification system for the various variants of mastocytosis recognized in the updated WHO classification.

Table 5: WHO Variants of Mastocytosis

Mastocytosis Variant
1 Cutaneous mastocytosis (CM) a) Maculopapular CM b) Diffuse CM c) Mastocytoma of skin
2 Indolent systemic mastocytosis a) Smoldering SM b) Isolated bone marrow mastocytosis
3 Systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)
4 Aggressive systemic mastocytosis With eosinophilia
5 Mast cell leukemia (MCL) Aleukemic MCL
6 Mast cell sarcoma
7 Extracutaneous mastocytoma

In this classification, the SM variant described in the table as SM-AHNMD describes the patients with associated FIP1L1-PDFGRα fusion kinase detected on mutational analysis.

3.0 SIGNIFICANT FINDINGS FROM OTHER 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_014\2006-2-28\

4.2 Table of Clinical Studies

Published clinical studies are summarized in **Table 6.** There were 25 SM patients in the published studies (28 patients with aggressive disease; 1 patient of Pardanani and one of Pottier had indolent SM). In addition, a phase II open label study [B2225] in patients with malignancies known to be associated with one or more imatinib-sensitive tyrosine kinases included 5 SM patients.

Table 6: Published Clinical Studies

Study	No. of patients treated with imatinib	Genotypic mutations	Imatinib Dose (mg/day)
Pardanani, et al (2003a)	12	c-Kit activating	100 – 400
Pardanani, et al (2003b)	5 patients, all reported in Pardanani, et al (2003a)	FIP1L1-PDGFRα, c-Kit activating	100 – 400
Pottier, et al (2003)	1	Not described	400
Akin, et al (2004)	1	Phe522Cys	400
Elliott, et al (2004)	1	FIP1L1-PDGFRα	100 – 400
Hennessy, et al (2004)	3 (out of 18 patients in total)	Not sought	200 – 400
Musto, et al (2004)	1	D816V	400
Pardanani, et al (2004a)	7 patients,3 already reported in Pardanani, et al (2003a)	FIP1L1-PDGFRα	100
Agis, et al (2005)	1	D816V	400
Zhang, et al (2005)	1	K509I	400
Total	**25**		

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

DSI inspections are planned.

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice. The phase II clinical study was monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

4.6 Financial Disclosures

No clinical investigators in study 2225 are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are identified on the spreadsheets by bolding the investigators name and are detailed in the disclosure forms that follow [FDA Form 3455]. These arrangements and interests were as follows (**Table 7**):

Table 7: Financial Disclosure Information

Investigator	Center No.	Amount Disclosed	Category of Disclosure
		>$25,000	
		>$25,000	
		$145,000	

b(6)

Financial disclosure information regarding the publications supporting this NDA submission was determined directly from the publication disclosure statements. The Authors either did not describe financial interest in any of the publications or stated that they had no conflict of interest or financial interest.

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 (Proposed)

b(4)

6.1.1 Methods

Clinical information concerning trial B2225 and the 23 referenced case reports were reviewed.

6.1.2 General Discussion of Endpoints

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

6.1.3 Study Design

Study B2225 is an open label, multicenter, phase II clinical trial testing the efficacy and safety of imatinib in patients suffering from life threatening diseases associated with Abl, Kit or PDGFR TKs. Patients had disease that was refractory to standard therapeutic options or for which no conventional therapies of definitive benefit existed. Tissue samples were to be collected and analyzed when possible and provided results to support the possible functional significance of one or more of the relevant imatinib-sensitive TKs. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, adequate end organ function, life expectancy of more than 3 months, adequate contraception and written, informed consent. Although patients were to have had a fresh tissue biopsy prior to study treatment and an additional biopsy while undergoing treatment, this was inconsistently done. Patients with hematologic malignancies (e.g. AML/myelodysplasia who displayed cytopenia) were eligible for the study despite thrombocytopenia and low absolute neutrophil count (ANC) if approved by Novartis after discussion with the investigator. Excluded from the study were patients eligible for other imatinib clinical protocols, treated with any other investigational agents within 28 days of first day of study drug dosing, had another primary malignancy or having received chemotherapy within 4 weeks (6 weeks for nitrosourea, mitomycin-C or any antibody therapy) prior to study entry. Patients were enrolled in the study over a 47-month period from 5-Feb-2001.

The planned starting dose differed between the two groups of malignancies, with the 45 patients with hematological malignancies initially receiving imatinib at 400 mg p.o. daily with a provision for a dose increase up to 800 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 4 weeks of therapy. The other 140 patients with solid tumors initially received imatinib at 800 mg p.o. daily with a provision for a dose increase up to 1000 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 8 weeks in solid tumor of therapy. Provisions for dose modification were included in the study protocol. Treatment was originally to be continued for 2 years; the protocol was later amended to allow indefinite treatment for patients benefiting from treatment in absence of safety concerns.

The primary objective of the study was to assess the efficacy of imatinib. The B2225 clinical study protocol as well as the published studies did not specifically distinguish between hematological and cytogenetic response as primary or secondary efficacy end-point, but hematological response was always used as primary endpoint, at least based upon the temporal evolution of events. Of note, no definition of response was included in the protocol for hematologic malignancies; the activity of imatinib was assessed primarily by evaluating normalization of blood counts and of bone marrow appearance, as well as cytogenetic analysis, FISH analysis for detection of PDGFR rearrangement and PCR analysis for its characterization.

Because these criteria used to asses the peripheral blood and the bone marrow response correspond to the definition of complete hematological and complete cytogenetic response used in other hematological malignancies, they are felt adequate to define the therapeutic efficacy of the drug in the disease, and were used in all the case reports published and included in this application.

The defined secondary endpoint in was the ECOG status. No secondary endpoint was specified in the published case reports, although cytogenetic response could be also considered as a secondary endpoint.

Other secondary objectives were to assess the safety and tolerability of imatinib, to evaluate the pharmacokinetic (PK) profile of imatinib in selected patients and to assess, if feasible, the functional significance of relevant signal-transduction components in target tissues by evaluating the expression and activation status of the relevant tyrosine kinase molecules or associated signaling molecules, by measuring indices of cellular proliferation and by correlating the changes in the above findings with clinical outcomes. However, due to the inconsistent collection of biological samples, these latter secondary objectives were not evaluated.

Five to ten patients per indication, condition, or disease were initially enrolled. Lack of clinical efficacy excluded future patients with the same indication, condition or disease from the study. If however, evaluation of the results of the first five patients suggested a positive effect of imatinib by conventional clinical response criteria or other pharmacodynamic measures (e.g. decrease in 18-fluorodeoxyglucose (18-FDG) uptake by positron emission tomography (PET) scanning), additional patients with the same disease could have been enrolled into the study in order to enable adequate evaluation of imatinib effects.

6.1.4 Efficacy Findings

Study B2225 investigators are listed in **Table 8**.

Table 8: B2225 Investigators

Center	Principal Investigator	Study Facility	City, State	Country
101	Prof. Allan Van Oosterom	UZ Gasthuisberg dienst oncologie	Leuven	Belgium
201	Prof. Jane Apperley Prof. John Goldman	Hammersmith Hospitals Dept. of Hematology	London	United Kingdom
301	Dr. Luca Gianni	Istituto Nazionale Tumori	Milano	Italy
401	Dr. Jaap Verweij	Rotterdam Cancer Institute	Rotterdam	Netherlands
501	Dr. George Demetri	Harvard Medical School	Boston, MA	USA
503	Dr. Bart Barlogie	University of Arkansas	Little Rock, AR	USA
504	Dr. Michael Heinrich	Oregon Health Sciences Univ	Portland OR	USA
505	Dr. Robert Shepard	UVA Health System	Charlottesville VA	USA
601	Prof. Heikki Joensuu	Helsinki University Central Hospital	Helsinki	Finland

701	Dr. Denis Soulieres	Centre Hospitalier Universitaire de Montreal	Montreal (Quebec)	Canada
702	Dr. Hal Hirte	Hamilton Regional Cancer Centre McMaster University Medical Centre	Hamilton Ontario	Canada
801	Dr. Richard Herrman	Unikliniken Kantonsspital Basel	Basel	Switzerland
901	Dr. Grant McArthur	Peter MacCallum Cancer Institute	Melbourne	Australia

Demographics for Study B2225 SM patients are summarized in **Table 9.** No cytogenetics information was obtained for these patients.

Table 9: Demographics Characteristics – Study B2225, SM patients

Demographic variable		Total (N = 5)
Sex – n (%)	Male Female	4 (80.0) 1 (20.0)
Race – n (%)	Caucasian	5 (100)
Age groups – n (%)	< 65 years ≥ 65 years	2 (40.0) 3 (60.0)
Age (years)	Mean (±SD) Range	65.0 (10.02) 49 – 74

Among the 5 patients with SM in study 2225 there were 1 PR, 1 SD and 3 unknown responses **(Table 10)**. Time to progression is summarized in **Table 11**. The median duration of therapy for the 5 patients was 13 months with a range of 43 to 680 days.

Table 10: Best overall responses – Study B2225, SM patients

Best response	**n**	**%**
Partial response (PR)	1	20.0
Stable Disease (SD)	1	20.0
Unknown	3	60.0

Table 11: SM - Best response and duration patients

Country/Center/ Subject	**Best response**	**Time to progression (days)**	**Duration of response**
GBR/201/162	PR	680+	127
GBR/201/165	UNK	1+	
GBR/201/174	UNK*	402	
USA/501/118	UNK	1+	
AUS/901/125	SD	170+	

PR = Partial response, SD = Stable disease, UNK = unknown.
* Best response required that responses be accurately coded on two successful visits for confirmation. Otherwise it is listed officially as "Unknown". This patient was felt by the investigator to have responded and was kept on therapy.

Response and response duration of literature SM patients is described in **Table 12.**

Table 12: Literature SM Patients-Characteristics, Response and Response Duration

N of pts	Sex	Age	MCD type	Mutation detected	Chic-2 deletion	Daily Dose (mg	Response	Response duration (mo)
Pardanani, et al (2003a) and Pardanani, et al (2003b)								
12	M	46	SM-eos	FIP1L1	Yes	100	Complete	10+
	M	31	SM-eos	FIP1L1	Yes	400 → 100	Complete	19+
	M	72	SM-eos	FIP1L1	Yes	100	Complete	1+
	F	78	SM-eos	D816V	No	100 → 400	None	
	F	85	SM-eos	D816V	No	100 → 400	None	
	F	45	SM	None	ND	100	Partial	10.5+
	M	70	SM	None	ND	400	Partial	8+
	M	61	SM	None	ND	NR	PD	
	NR	NR	SM	None	ND	NR	None	NR
	NR	NR	SM	None	ND	100 → 400	Partial	NR
	NR	NR	SM	None	ND	100 → 400	Partial	NR
	NR	NR	SM	None	ND	NR	None	
Pottier, et al (2003)								
1	M	32	SM-eos		ND	400	Complete	6+
Akin et al (2004)								
1	F	25	SM	Phe522Cys	ND	400	Partial	7+
Elliott, et al (2004)								
1	M	30	SM-eos	FIP1L1	ND	400 → 100	Complete	19+
Hennessy, et al (2004)								
3	F	64	SM	ND	ND	NR	None	NR
	F	42	SM	ND	ND	400	Partial	NR
	M	80	SM	ND	ND	200	Partial	NR
Musto, et al (2004)								
1	M	33	SM	D816V	ND	400	PD	
Pardanani, et al (2004a)								
7	M	46*	SM-eos	FIP1L1	Yes	100	Complete	18+
	M	30*	SM-eos	FIP1L1	Yes	100	Complete	28+
	M	72*	SM-eos	FIP1L1	Yes	100	Complete	9+
	M	49	SM-eos	FIP1L1	Yes	100	Complete	5+
	M	51	SM-eos	FIP1L1	Yes	100	Complete	4+
	M	50	SM-eos	FIP1L1	Yes	100	Complete	30+
	M	26	SM-eos	FIP1L1	Yes	100	Complete	7+
Agis, et al (2005)								
1	F	43	SM	D816V		400	Complete	NR
Zhang, et al (2005)								
1	F	46	SM	K509I		400	Partial	NR

NR Not recorded; ND not done; PD = progressive disease; SM = systemic mastocytosis; SM-eos = SM with eosinophilia; FIP1L1 = FIP1L1/PDGFRα fusion

* These patients likely were previously reported by Pardanani, et al (2003a) based on patient age and enrollment data. Additional response duration is provided in this publication.

Table 13 presents a summary of cytogenetic abnormalities and treatment response.

Table 13: Cytogenetic Abnormalities and Treatment Response

Cytogenetic Abnormality	Number of Patients	Best Response	Duration (months at time of reports)
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)			
Elliott, et al (2004)	1	1 Complete	19+
Pardanani, et al (2003a)	3	3 Complete	10+, 19+, 1+
Pardanani, et al (2004a)	4	4 Complete	5+, 4+, 30+, 7+
Total	8	8 Complete	
Juxtamembrane mutation			
Zhang, et al (2005)	1	1 Partial	24+
Akin, et al (2004)	1	1 Partial	7+
Total	2	2 Partial	
D816V mutation			
Pardanani, et al (2003b)	2	None	NA
		None	NA
Musto, et al (2004)	1	None	NA
Agis, et al (2005)	1**	1 Complete	18+
Total	4	1 CR	
Unknown or no cytogenetic abnormality detected			
Pardanani, et al (2003b)	7	4 Partial	10+, 8+
		1 None	11 weeks
		1 Unknown	NA
		1 Death unrelated to study drug	10 days
Hennessy, et al (2004)	3	2 Partial	NA
		1 None	NA
Pottier, et al (2003)	1	1 Complete	6+
Novartis B2225	5	1 Partial	
		1 Stable disease	
		3 Unknown***	
Total	16	1 CR, 7 PR, 1 SD	
Overall Total	30	10 Complete, 9 Partial	

** After 6 months of therapy the patient was in complete cytogenetic remission. *** Best response required that responses be accurately coded on two successive visits for confirmation. Otherwise it was listed officially as "Unknown". One patient with "Unknown" as Best Response was felt by the investigator to have had PR and was kept on therapy.

All eight SM patients with the FIP1L1-PDGFRα fusion kinase detected either by direct RTPCR mutational analysis or by FISH-based detection of the CHIC2 locus deletion (as a surrogate for the presence of the fusion kinase) achieved sustained CR or PR with imatinib therapy for up to 30+ months. Likewise, the detection of an activating kinase mutation in the juxtamembranous "control" region of the tyrosine kinase is also a good predictor of a beneficial response to imatinib therapy. The 2 patients with

juxtamembranous mutations in the published literature had sustained PR for up to 24+ months. When detected, patients with FIP1L1-PDGFRα fusion kinase or juxtamembranous mutations exhibited a 100% response rate to imatinib, with response durations of 1+ to 30+ months. Sixteen patients out of 30 had unknown or no detected cytogenetic abnormality. Of these patients, 8 (50%) achieved sustained response for up to 10+ months.

Literature SM patients are summarized below:

Pardanani, et al (2003a): Responses to imatinib were assessable in 10 out of 12 patients with mast cell disease (MCD). Imatinib was given at dose of 100-400 mg/day to 12 patients with MCD. Patients not responding to lower imatinib doses were eventually all treated with 400 mg/day. Five patients (one indolent and four with aggressive disease) had associated eosinophilia (eosinophils > 1500/μL). Three of these five patients, negative for Asp816Val mutation, had striking response on 100 mg/day imatinib within few days and CCR within 12 weeks. The patients were maintained at 100 mg/day imatinib. Two patients with elevated eosinophil count were refractory to imatinib at 400 mg/day both were c-Kit Asp816Val positive. The seven MCD patients not associated with peripheral blood eosinophilia were all c-Kit Asp816Val-negative. At 6 months follow-up, two patients with aggressive MCD (refractory to 2-chlorodeoxyadeosine chemotherapy or interferon-α) had important mast-cell cytoreduction when treated with 100 mg/day or 400 mg/day, respectively; two other patients with indolent MCD with predominantly cutaneous manifestations had complete CCR and CHR. These results suggest that imatinib either inhibits the growth-promoting role of wild type c-Kit, or targets an unknown oncogenic tyrosine kinase.

Pardanani, et al (2003b): This was a new publication on five patients already described in the earlier Pardanani, et al (2003a). In this report the patients were examined for the presence of the FIP1L1 fusion to the PDGFRα gene (FIP1L1-PDGFRα). Additionally, this fusion gene was detected by a FISH test identifying the chromosome deletion at CHIC2 that results in the fusion kinase formation. The three patients who had SM-eos and who had responded to imatinib therapy with complete clinical and hematological responses all showed a loss of one of the CHIC2 alleles by one color FISH testing of interphases, thus confirming the presence of the FIP1L1-PDGRFα. The other two patients had the D816V mutation, lacked CHIC2 allele loss and did not respond to imatinib.

Pottier, et al (2003): Described a 32 year old male patient diagnosed with an idiopathic HES associated with cutaneous mastocytosis. After failure of interferon-α and hydroxyurea therapy, CCR and CHR were induced within 3 weeks by imatinib treatment at 400 mg/day. The urticaria pigmentosa lesions persisted. The patient was continuing on therapy improved after six months.

Akin, et al (2004): Described a 25 year old female patient with SM with c-Kit Phe522Cys mutation. After non-response to treatment with interferon-α, imatinib was initiated at

increasing does up to 400 mg/day. Bone marrow analysis after 2 months of treatment revealed a notable reduction on the extent of bone marrow mast cell infiltration. Serum tryptase levels decreased from 173 ng/mL to 115 ng/mL after 4 doses of 100 mg/day imatinib, and to 21.5 ng/mL after approximately 3.5 months on 400 mg/day; they remained at 20 ng/mL as of 7 months on treatment.

Elliott, et al (2004) described a patient with SM-eos. A 30 year old male patient presented with a 5 month history of fatigue, fever, night sweats and a 20 kg weight loss. He was found to have splenomegaly, anemia and leukocytosis with 16% eosinophils. Screening for cardiac disease was negative. A prolonged course of hydroxyurea led to profound pancytopenia and transfer to another hospital. Bone marrow examination showed hypercellularity and aggregates of c-Kit (CD117) and tryptase positive atypical mast cells. Flow cytometry revealed coexpression of CD117 and CD25, but not CD2. PCR analyses for c-Kit mutations were negative for D816V and V459G. The patient was treated with interferon-α, but did not improve. Imatinib was begun at 400 mg/day. Leukocyte counts improved within two days with normalization of the leukocyte and eosinophil counts within 5 days. After one week of therapy the imatinib dose was reduced to 100 mg/day. By six weeks the patient was in a complete clinical remission. At three months a bone marrow examination was performed and was normal. The patient had remained in complete remission for 19 months at the time of the report and continued to receive imatinib. Archival tissue revealed the presence of FIP1L1- PDGFRα mutation.

Hennessy, et al (2004): summarized the MD Anderson experience for patients with SM coming to their institution from 1944-2002. Eighteen cases were identified with the authors noting that mastocytosis had not been traditionally classified as a malignancy and that MD Anderson is not a reputed center for its treatment. Three of these patients received imatinib at some point during their treatments and two of the three patients were reported to have responded, but the completeness and duration of the responses were not reported. The authors did note that none of these patients had associated eosinophilia.

Musto, et al (2004): Described a 33 year old male patient with a 3-year history of aggressive, sporadic SM treated with imatinib at 400 mg/day. After 16 weeks of therapy, neither improvement of the clinical symptoms nor reduction of mastocytic infiltration was observed, and the treatment was stopped. Later retrospective analysis of archival tissue revealed the presence of the c-Kit D816V mutation.

Pardanani, et al (2004a): the authors further expanded their investigations by identifying 89 consecutive patients, either prospectively or retrospectively, who had the database string of "eosinophilia", "hypereosinophilic syndrome", "eosinophilic leukemia" or "mast cell disease". Following central re-review of histories and diagnostic material the cases were classified into "HES (57 patients, 64%)", "systemic mast cell disease with associated eosinophilia (SMCD-eos) (19 patients, 21%)", "chronic eosinophilic syndrome (5 patients, 6%)" and "reactive eosinophilia (8 patients, 9%)". Ten of the patients with SMCD-eos had CHIC2 deletion and seven of these patients received imatinib at a dose of

100 mg/day. All experienced a complete clinical and hematological remission rapidly and all were in continuing response and therapy at the time of the report. The authors also pointed out that the mast cell infiltrations of the bone marrow in patients with CHIC2 deletions tended to be more diffuse with only small aggregates (10 to 30 cells) of tryptase positive mast cells. Of the 9 patients in the series who had SMCD-eos but did not show the CHIC2 deletion, three carried the D816V mutation. Five of these patients with SMCD-eos and no CHIC2 deletion detected received imatinib, but none were reported to respond (the mix of D816V mutations in this group is not reported). Interestingly, all 10 patients with SMCD-eos and a CHIC2 deletion were males, whereas 6 of 9 patients with no CHIC2 deletion were females. In this publication the sponsor was able to identify 7 additional patients with SMCD-eos and CHIC2 deletion that had previously been reported by the authors (matched by reported age and date of diagnosis), but we were unable to tell whether the SMCD-eos without CHIC2 deletions were represented by earlier case reports or not. We surmise that two of these seven patients were previously reported and that three of these total patients received imatinib without response.

Agis, et al (2005): Reported a 43 year old female patient with typical Ph+ CML in whom a co-existing bone marrow mastocytosis, a special variant of SM, was diagnosed. The marrow demonstrated positive staining for tryptase in the mast cells and the spindle shaped cells in the marrow were immunoreactive for CD117 and CD25. c-Kit point mutational analysis using microdissected cells from the bone marrow. PCR analysis of the microdissected mast cells showed the presence of the D816V mutation. The patient was begun on imatinib at 400 mg/day. After six months of therapy the patient was in complete cytogenetic remission as well as had cleared her bone marrow of mast cell infiltrates. After 18 months of therapy the patient remained in complete remission of both diseases and had a normal serum tryptase level.

Zhang, et al (2005): Reported a case of familial mastocytosis without D816V mutation but where a novel K509I mutation in exon 9 was present. The mother, age 26, developed worsening symptoms. Her bone marrow WBCs were sensitive to imatinib in vitro and the patient was subsequently started on imatinib at a dose of 400 mg/day. Her liver function improved with a drop in ALT, alkaline phosphatase and γGT levels. Her liver reduced in size from 10 to 6 cm below the costal margin.

Secondary efficacy results

The secondary end-point evaluated for efficacy was the ECOG status. In the overall population, the ECOG performance status worsened at study end in most of the patients, which is to be expected considering that the majority of the patients left the study because of unsatisfactory results corresponding to progressive disease in most cases. The ECOG performance status for the SM population is not different to that of the overall population, but the small number of patients prevents from performing in-depth analysis.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

One uncontrolled study (B2225) enrolling 5 patients and ten publications including 25 SM patients (23 aggressive SM) support the efficacy claim. Eight out of the 28 patients with aggressive SM (30%) experienced a complete hematological response. In Study B2225 one patient had a confirmed partial response, a second patient had an unconfirmed partial response, and one further patient experienced stable disease as best overall response. In the published literature, eight patients experienced a partial response. Overall, counting confirmed complete and partial responders, imatinib induced a hematological response in 17 out of 28 patients (61%). In addition to improvement in hematologic and bone marrow abnormalities there were also improvements in symptomatology and other organ dysfunction abnormalities.

Cytogenetic abnormalities were evaluated in 20 of the 23 patients with aggressive SM treated in the published reports. Seven out of these 20 patients had FIP1L1-PDGFRα fusion kinase, as determined either by actual mutational analysis showing FIP1L1-PDGFRα fusion kinase or by a CHIC2 allele deletion detected by FISH methodology implying presence of the FIP1L1-PDGFRα fusion kinase. Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their SMCD. Two patients showed a c-Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I). Patients that harbor the D816V mutation of c-Kit are not sensitive to imatinib. All 7 patients with the FIP1L1-PDGFRα fusion kinase had a CHR.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology and chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsened after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form only if the patient received study treatment. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy, when they

were recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Any Adverse Event occurring after the study completion and within four weeks of last drug intake was recorded on the Adverse Event CRF page.

Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also had to be reported to Novartis within 24-hours of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:
1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. was significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
Any pregnancy or fathering the child during the study will be considered as an SAE for the purpose of study reporting.

Events not considered serious are hospitalizations occurring under the following circumstances: planned before entry into the clinical study; for elective treatment of a preexisting hospitalization (unless fulfilling the criteria above); routine treatment or monitoring of the study indication and not associated with any deterioration in condition.

Any SAE occurring within four weeks after completion of the study has to be reported and recorded. In addition any pregnancy within 84 days (12 weeks, 3 months) after the last STI571 intake has to be reported and recorded as an SAE.

The institution performed laboratory analyses according to the Visit Schedules.
At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page in addition to the appropriate laboratory CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF. AE's are summarized in **Table 14**.

Table 14: Adverse events regardless of study drug relationship

SM patients N = 5	
Preferred term	**n (%)**
Diarrhea	4 (80.0)
Nausea	4 (80.0)
Ascites	3 (60.0)
Dyspnea	3 (60.0)
Muscle cramp	3 (60.0)
Fatigue	2 (40.0)
Edema peripheral	2 (40.0)
Anemia	2 (40.0)
Pruritus	2 (40.0)
Rash	2 (40.0)
Lower respiratory tract infection	2 (40.0)

7.1.1 Deaths

One patient with SM died on study, patient 201/165, a 73 year old male, who died of unknown causes.

7.1.2 Other Serious Adverse Events

One SM patient 501/118 developed a grade 4 splenic infarction on day 42.

7.1.3 Dropouts and Other Significant Adverse Events

In SM patients, there was only one instance of CTC grade 3 alkaline phosphatase increase. No SM patient was withdrawn from the study due to abnormal laboratory values.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

See Table 14

7.1.6 Laboratory Findings

See Table 14

7.1.7 Vital Signs

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

7.1.8 Electrocardiograms (ECGs)

No ECGs were performed for the MDS study.

7.1.9 Immunogenicity

There is no new relevant information.

7.1.10 Human Carcinogenicity

There is no new relevant information.

7.1.11 Special Safety Studies

There is no new relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Gleevec has no known potential for abuse..

7.1.13 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
- PSUR 7 covering the period 11 May 2005 - 10 May 2006
- 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 "Sweet's Syndrome" was proposed for inclusion to the BPI.

In 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 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.

In PSUR 7 and in a recent literature report congestive heart failure and left ventricular dysfunction associated with Gleevec treatment were updated. A recent article published online in Nature Medicine (Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine; advance online publication July 23rd. 2006) reported 10 Gleevec treated patients who developed severe congestive heart failure and left ventricular dysfunction. Supplemental data available on the Nature Medicine website show that prior to Gleevec treatment all 10 patients had New York Heart functional class 1 and normal left ventricular ejection fractions. Some of these patients had pre-existing conditions including hypertension, diabetes and coronary artery disease. In an abstract published in the Journal of Cardiac Failure (Iliescu C, Wamique Yusuf S, Auerbach L, et al. Impact of angiotensin converting enzyme inhibitors & carvedilol on recovery of cardiac function in imatinib associated cardiomyopathy. Journal of Cardiac Failure 2005; 40 No. 6 Suppl. Abstract 054. 9th Annual Scientific Meeting of the Heart Failure Society of America, Sept 18-21st 2005) the authors stated that treatment with angiotensin converting enzyme inhibitors (ACE-I) and carvedilol resulted in significant improvements in left ventricular ejection fraction (LVEF) and New York

Heart Association (NYHA) Class. Three of these patients, when re-challenged, were reported to have no further diminution of cardiac function.

The Nature Medicine article also reports on preclinical studies showing that Gleevec treated mice develop left ventricular contractile dysfunction. Gleevec also induces cell death in isolated cardiomyocytes. The authors hypothesize that development of cardiac dysfunction is related to inhibition of the Abl receptor and may be a possibility with any drug that targets the Abl receptor.

A thorough review of the sponsor's safety database yielded 148 spontaneous cases of cardiac events. The median age was 65 years. Of 117 patients with sufficient clinical information for analysis approximately 50% had a history of cardiovascular disease before the onset of Gleevec treatment (mostly hypertension and ischemic heart disease), 40% were on cardiac medications and 8.5% experienced worsening of preexisting heart disease.

Thus heart failure is a recognized, potentially severe, but uncommon complication of Gleevec therapy. Current information does not support routine screening and monitoring of cardiac function in patients taking Gleevec. Any patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with symptoms consistent with cardiac failure should be aggressively evaluated and treated.

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

Patients with SM had a median exposure of 13.0 months (max 22.3 months).

Intensity of exposure to study drug is shown in **Table 15.**

Table 15: Intensity of exposure

Absolute Dose Intensity (mg/day) [1]	SM patients N = 5
Mean ±SD	214.2 ±169.49
Median	155.9
Min – Max	19.6 – 393.2

[1] Total dose over the course of the trial/total number of days in trial

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 studied.
Doses and durations of exposure were adequate to assess safety for the intended use.
Study design 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

Safety of imatinib has been best evaluated in phase II trials in CML. The majority of CML patients experienced drug-related adverse events (AEs) at some time, but most were mild to moderate in severity. Discontinuation for drug related AEs occurred in 2%, of patients in chronic phase CML. 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). Gleevec associated myelosuppression was 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. The data indicate that the drug is well tolerated in the target population.

The currently reported AE's in patients with SM are similar to the above known Gleevec adverse effects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Separate safety data was provided for each study. Because of different Gleevec doses, because of the small number of patients studied in each report and because of the large amount of safety data already available it was not felt to be worthwhile to pool safety data. .

7.4.2 Explorations for Predictive Factors

Predictive factors including dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions were not explored in the current study.

7.4.3 Causality Determination

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

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 100mg/day to 400 mg/day for adult patients with SM.

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

In accordance with 21 CFR 314.55 the sponsor requests a full waiver of the requirements for submission of data that are adequate to assess the safety and efficacy of Gleevec in this population of pediatric patients. The basis for this waiver is 314.55c(2)(ii): necessary studies are impossible or highly impractical because the number of patients is so small.

8.5 Advisory Committee Meeting

An ODAC meeting to discuss this application is not planned.

8.6 Literature Review

Agis H, Sotlar K, Valent P, et al (2005) Ph-chromosome-positive chronic myeloid leukemia with associated bone marrow mastocytosis. Leuk Res; 29:1227-32.

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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.

Based upon cumulative reviews in the most recent PSUR version 7 it was recommended to continue to monitor the following events: Congestive heart failure and left ventricular dysfunction.

8.8 Other Relevant Materials

No new information is available.

9.0 OVERALL ASSESSMENT

9.1 Conclusions

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

9.2 Recommendation on Regulatory Action

The medical reviewer recommends that regular approval be granted for the following indication:. "Gleevec is indicated for the treatment adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with cKit mutational status unknown". Approval does not include patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), patients with SM and an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Gleevec and should not receive Gleevec.

The rarity of occurrence of aggressive SM with absent c-Kit D816V mutation makes randomized trials impractical. The number of patients suffering from smoldering and aggressive SM in the USA is estimated to be 20,000, among which 8,000 are adults and 12,000 children. Kit D816V mutation is present in approximately 60% of the adults, leaving 3000 adults without D816V mutation. Aggressive mastocytosis represents less than 5% of adult cases or less than 150 patients.

The Gleevec team is reviewing 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

Assure availability of a validated test kit for detection of the D816V c-kit mutation. An IDE or Pre-Market Application filing by Novartis or a 3rd party should occur no later than 4 months after Gleevec approval for this indication.

9.4 Labeling Review

Label reviewed by DODP Gleevec team.

9.5 Comments To Applicant

To expand the indication to indolent variants of SM randomized trial(s) will be necessary.

10.0 APPENDICES

10.1. Review Of Individual Study Reports

See clinical section

10.2 Line-By-Line Labeling Review

Done.

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Application Type	NDA 21-588
Submission Number	SE1
Submission Code	017 (Hypereosinophilic syndrome)
Letter Date	3/28/06
Stamp Date	3/28/06
Reviewer Name	Martin H. Cohen, M.D. Shenghui Tang, Ph.D.
Review Completion Date	6/10/06
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	S

Formulation

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

Dosing Regimen

For patients with HES/CEL the recommended dose of Gleevec is 400 mg/day. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

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(s)

Proposed Indication: Gleevec is indicated for the treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL). (4)

Other Indications: 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 proposed indication.

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1.0 EXECUTIVE SUMMARY

The purpose of the present submission is to present data to support the proposed indication: "Gleevec is indicated for the treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL).

One open-label, multicenter, Phase II clinical trial (study B2225) was conducted. This study included 14 patients with HES and CEL. In addition a literature review found 35 publications summarizing 162 HES/CEL patients. The HES/CEL patients were generally treated with Gleevec 100 mg to 400 mg daily.

Recommendation On Regulatory Action

The medical reviewer recommends that regular approval be granted. Clinical benefit is demonstrated by long duration responses. The overall CHR rate was 61% and the PHR rate was 9%. Response durations for the 4 HES PR's in study B2225 were at least 348, 394, 131 and 183 days and response durations in literature patients ranged from 1.5+ months to 44 months. In addition, the rarity of occurrence of HES with or without demonstrated FIP1L1-PDGFRα fusion kinase makes randomized trials impractical.

Availability of an assay for the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) is necessary because the Gleevec starting dose for such patients is 100 mg/day.

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

None

1.23 Other Phase 4 Requests

Assure availability of a validated test kit for detection of the FIP1L1-PDGFRα fusion kinase, as determined either directly by mutational analysis or by demonstration of a CHIC2 allele deletion by FISH methodology that implies the presence of the FIP1L1-PDGFRα fusion kinase. The Pre-Market Application (PMA) filing by a 3rd party should occur 3 months after approval.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

One open-label, multicenter, Phase II clinical trial (study B2225) was conducted. This study included 14 with patients with HES/CEL. This application is supported by 35 publications summarizing 162 patients. Thus the total number of patients included in this application is 176. The HES/CEL patients were generally treated with 100 mg to 400 mg of Gleevec daily. The age of HES patients in trial B2225 ranged from 16 to 64 years. The age of literature patients ranged from 11 to 78 years..

1.3.2 Efficacy

Of the 176 patients treated for HES/CEL, 107 (61%) achieved a complete hematologic response (CHR) and 16 (9%) a partial hematologic response (PHR) (70% overall response rate). Cytogenetic abnormalities were evaluated in 117 of the 176 patients treated in the published reports (none in study B2225). Out of these 117 patients, 61 were positive for FIP1L1-PDGFRα fusion kinase. All these FIP1L1-PDGFRα fusion kinase positive patients achieved a CHR. The FIP1L1-PDGFRα fusion kinase was either negative or unknown in 115 patients (including B2225 patients), of which 62 (54%) achieved either a CHR (n=46) or a PHR (n=16).

Additionally, improvements in symptomatology and other organ dysfunction abnormalities were reported by the investigators in the case reports. Improvements were reported in cardiac, nervous , skin/subcutaneous tissue, respiratory/thoracic/mediastinal, musculoskeletal/connective tissue/vascular, and gastrointestinal organ systems.

1.3.3 Safety

Imatinib treatment was well tolerated by patients with HES. The safety profile in this small patient population does not seem different from the known safety profile of imatinib observed in other larger hematologic malignancies populations, such as CML. All patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematologic abnormalities were also frequent, with instances of CTC grade 3 leukopenia, neutropenia, lymphopenia and anemia.

In patients with hypereosinophilic syndrome (HES) and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Follow-up, to-date indicate that the following toxicities may be of concern:

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome. In some reported cases a recurrent dermatologic reaction was observed upon rechallenge. Several 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. 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. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST. There have been post-marketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with Gleevec.

Gastrointestinal Disorders: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

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. 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. In patients with hypereosinophilic syndrome and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Systemic mastocytosis might also be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in both HES and SM patients who have high eosinophil levels. If either is abnormal, prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Gleevec.

Toxicities From Long-Term Use: Potential toxicities suggested by animal studies, include 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).

1.3.4 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 100 mg/day to 400 mg/day for adult patients with HES/CEL.

1.3.5 Drug-Drug Interactions

CYP3A4 Inhibitors: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin).may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

CYP3A4 Inducers: 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.

CYP3A4 Substrates: 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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment at imatinib doses ranging from 100-800 mg (**Table 1**). Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

Test	Normal (n=14)	Mild (n=30)	Moderate n=20	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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.

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 Abl tyrosine kinase at the in vitro, cellular, and in vivo level. The compound specifically inhibited proliferation of v-Abl and Bcr-Abl expressing cells, suggesting that it is not a general antimitotic agent. In colony formation assays using progenitor cells ex vivo from patients with CML, imatinib showed selective inhibition of Bcr-Abl positive colonies. In addition, imatinib potently inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ), c-Kit, the receptor for stem cell factor (SCF), c-Fms, the receptor for macrophage stimulating factor (M-CSF), as well as Abl and Arg PTK. Imatinib also inhibits the cell signaling events mediated by activation of Bcr-Abl, c-Kit and the PDGF receptors. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor, insulin and phorbol esters. In vivo, the compound shows anti-tumor activity as a single agent in animal models at well tolerated doses.

2.2 Currently Available Treatment For Proposed Indication

Systemic corticosteroid therapy is generally administered to symptomatic patients. If control is not achieved, other agents are added or used, including hydroxyurea, interferon-α, vincristine and alkylating agents. Pheresis, anticoagulation, cardiac surgery, splenectomy,and stem cell transplantation are considered when clinically appropriate

2.3 Availability Of Proposed Active Ingredient In The United States

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

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

The clinical results were discussed with the FDA on 12-Aug-2004. The objective of this meeting was to seek guidance for the approval of imatinib as a treatment for patients with rare malignancies carrying imatinib-sensitive targets. The FDA recognized the rarity of the targeted malignancies and accepted to consider a potential filing based upon an exploratory phase II study and published case reports/studies. Suggestions and recommendations on how to analyze and present the data were also given.

2.6 Other Relevant Background Information

Idiopathic hypereosinophilic disorder is a rare hematologic disorder characterized by chronic overproduction of eosinophils, tissue infiltration and organ damage. Diagnostic criteria include sustained eosinophilia (>1500 eosinophils/mm3) for more than six months, exclusion of reactive causes of hypereosinophilia such as parasitic infections or allergic reactions, and evidence of end organ involvement. Thus, HES originally was a recognized disorder that required the exclusion of other etiologies for its diagnosis. The criteria for the diagnosis of chronic eosinophilic leukemia are presented in **Table 2**.

Table 2: Criteria for the diagnosis of chronic eosinophilic leukemia

Eosinophil count at least 1500/mm3
Peripheral blood and bone marrow blast cells <20%
Criteria for atypical CML, CMML and Ph+ CML not met
Myeloid cells demonstrated to be clonal, e.g. by detection of a clonal cytogenetic or molecular genetic abnormality or by demonstration of very skewed expression of X chromosome genes

Eosinophils derive in the bone marrow from CD34+ myeloid progenitor stem cells and differentiate in response to a number of T-cell derived eosinophilic cytokines and growth factors including IL-3, GM-CSF and IL-5. Eosinophils participate broadly in a variety of functional roles, including host defense, allergic responses, and inflammatory reactions (including tissue injury and fibrosis). Clinically, these multiple functions lead to the protean manifestations of eosinophilic disorders. Under normal circumstances, there are many more eosinophils in the peripheral tissues than circulating in the blood. This predilection continues as hypereosinophilic disorders develop. Thus, the clinical manifestations of organ infiltration and subsequent dysfunction often dominate the clinical picture. Patients with HES have a predilection for organ infiltration of the heart, the central and peripheral nervous system, the lungs and the skin. The illness most often

develops in patients 20 to 50 years of age and has a strong male to female predilection (9:1 ratio). End organ manifestations are multiple as summarized in **Table 3**.

Table 3: Eosinophil End Organ Damage

System Organ Class*	Damage
Cardiac disorders	Constrictive pericarditis, endomyocardial fibrosis, myocarditis, intramural thrombi, valve regurgitation, cardiomyopathy
Nervous system disorders	CNS thromboemboli, peripheral neuropathy, CNS dysfunction, epilepsy, dementia, eosinophilic meningitis
Skin and subcutaneous tissue disorders	Angioedema, urticaria, papulonodular lesions, mucosal ulcers, vesicobullous lesions, microthrombi
Respiratory, thoracic and mediastinal disorders	Pulmonary infiltrates, lung fibrosis, pleural effusions, pulmonary emboli
Eye disorders	Microthrombi, vasculitis, retinal arteritis
Musculoskeletal and connective tissue disorders and/or vascular disorders	Arthralgia, joint effusions, polyarthritis syndromes, Raynaud's phenomenon, digital necrosis
Gastrointestinal disorders	Ascites, diarrhea, gastritis, colitis, pancreatitis, cholangitis, Budd-Chiari syndrome

*In addition to the system specific abnormalities, patients may also have unexplained constitutional symptoms of anorexia, weight loss, fever, excessive sweating and psychiatric disturbances

The most commonly encountered clinical events, and often the most serious, are the cardiovascular complications that occur in 50-75% of all patients. These are often life threatening and life limiting in patients with HES. In the early phases of cardiac involvement, eosinophilic infiltration can cause inflammatory disorders of the heart and intramural thrombi to form on the endocardial surfaces. With time inflammation leads to fibrosis leading to valvular disorders and constrictive pericarditis.

Modern treatment paradigms for HES, once appropriate diagnostic and extent of disease evaluations have been performed, employ algorithms for treatment based on the presence or absence of the FIP1L1-PDGFRα fusion gene. If the patient does not have the FIP1L1-PDGFRα fusion gene, no extreme eosinophilia in the peripheral blood, and no evidence of organ dysfunction, following the patient quarterly with re-evaluations is the currently accepted approach. If the disease is more extreme, then systemic corticosteroid therapies are generally administered using various regimens. If control is not achieved, other agents are added or used, including hydroxyurea, interferon-α, vincristine and alkylating agents. Pheresis, anticoagulation, cardiac surgery, splenectomy, stem cell transplantation, and investigational agents are included under specialized circumstances. When patients are demonstrated to have the FIP1L1-PDGFRα fusion gene, then a similar approach to management is recommended, but a trial of imatinib is recommended to be integrated into therapy considerations for the patient. Currently improved therapies and patient support have led to survival rates in the late 1980s reported as 80% at 5 years and 40% at 10 and 15 years.

3.0 SIGNIFICANT FINDINGS FROM OTHER 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_014\2006-2-28\

4.2 Table of Clinical Studies

Published clinical studies are summarized in **Table 4.** There were 162 HES/CEL patients in the 25 published studies. In addition, a phase II open label study [B2225] in patients with malignancies known to be associated with one or more imatinib-sensitive tyrosine kinases included 14 HES/CEL patients.

Table 4: HES - Literature Reports

Investigators	Number	Gleevec Dose
Schaller & Burkland (2001)	1	100 mg/day then 75 mg/day
Ault, et al (2002)	1	100 mg/day
Gleich, et al (2002)	5*	100 mg/day then 200 mg/week
Gotlib, et al (2002)	5	100-400 mg/day
Nolasco, et al (2002)	1	100 mg/day then 200 mg/week
Cools, et al (2003)	11	100-400 mg/day
Cortes, et al (2003)	9	100-400 mg/day
Ishhii, et al (2003)	1	100 mg/day
Koury, et al (2003)	1	200-400 mg/day
Pardanani, et al (2003)	5	100-400 mg/day
Pottier, et al (2003)	1	400 mg/day
Salem, et al (2003)	6	100 mg/day
Ascione, et al (2004)	1	400 mg/day
Frickhofen, et al (2004	1	200 mg/day
Klion, et al (2004)	7	300-400 mg/day
Malagola, et al (2004)	1	100 to 400 mg/day
Martinelli, et al (2004)	1	600 mg/day
Musto, et al (2004	4	600-800 mg/day
Payne, et al (2004)	2	100 mg/day
Rose, et al (2004)	1	200 mg/day
Rotoli, et al (2004)	1	200-400 mg/day
Smith, et al (2004)	3	400-600 mg/day
Tan, et al (2004)	1	100 mg/day
Vandenberghe, et al (2004)	5	100 mg/day
Wolf, et al (2004)	1	100 mg/day
Anghel, et al (2005)	1	200 mg/day

Cervetti, et al (2005)	1	100 mg/day
Imashuku, et al (2005)	1	100-200 mg/day
La Starza, et al (2005)	12**	100-600 mg/day
Musial, et al (2005)	1	100 mg/day for 3 months, then qod
Onitilo, et al (2005)	1	100 mg/day
Roche-Lestienne, et al (2005)	9	100-200 mg/day
Chung, et al (2006)	1	100 mg/day
Müller, et al (2006)	2	100-400 mg/day
Martinelli, et al (2006)	59	100-400 mg/day
Total	162	

* Including one patient already reported by Schaller & Burkland (2001)

** Including one patient already reported by Rotoli, et al (2003).

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

DSI inspections are planned.

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice. The phase 2 clinical study was monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

4.6 Financial Disclosures

No clinical investigators in study 2225 are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are identified on the spreadsheets by bolding the investigators name and are detailed in the disclosure forms that follow [FDA Form 3455]. These arrangements and interests were as follows (**Table 5**):

Table 5: Financial Disclosure Information

Investigator	Center No.	Amount Disclosed	Category of Disclosure
		>$25,000	
		>$25,000	
		$145,000	

b(6)

Financial disclosure information regarding the publications supporting this NDA submission was determined directly from the publication disclosure statements. The

authors either did not describe financial interest in any of the publications or stated that they had no conflict of interest or financial interest.

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 (Proposed)

b(4)

Gleevec is indicated for the treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL).

The approved indication should be for the treatment of adult HES patients who demonstrate either the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) as well as for HES patients who are FIP1L1-PDGFRα fusion kinase negative or unknown.

6.1.1 Methods

Clinical information concerning trial B2225 and the 35 referenced case reports were reviewed.

6.1.2 General Discussion of Endpoints

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

6.1.3 Study Design

Study B2225 is an open label, multicenter, phase 2 clinical trial testing the efficacy and safety of imatinib in patients suffering from life threatening diseases associated with Abl, Kit or PDGFR TKs. Patients had disease that was refractory to standard therapeutic options or for which no conventional therapies of definitive benefit existed. Tissue samples were to be collected and analyzed when possible and provided results to support the possible functional significance of one or more of the relevant imatinib-sensitive TKs. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG)

performance status 0 to 2, adequate end organ function, life expectancy of more than 3 months, adequate contraception and written, informed consent. Although patients were to have had a fresh tissue biopsy prior to study treatment and an additional biopsy while undergoing treatment, this was inconsistently done. Patients with hematologic malignancies (e.g. AML/myelodysplasia who displayed cytopenia) were eligible for the study despite thrombocytopenia and low absolute neutrophil count (ANC) if approved by Novartis after discussion with the investigator. Excluded from the study were patients eligible for other imatinib clinical protocols, treated with any other investigational agents within 28 days of first day of study drug dosing, had another primary malignancy or having received chemotherapy within 4 weeks (6 weeks for nitrosourea, mitomycin-C or any antibody therapy) prior to study entry. Patients were enrolled in the study over a 47-month period from 5-Feb-2001.

The planned starting dose differed between the two groups of malignancies, with the 45 patients with hematologic malignancies initially receiving imatinib at 400 mg p.o. daily with a provision for a dose increase up to 800 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 4 weeks of therapy. The other 140 patients with solid tumors initially received imatinib at 800 mg p.o. daily with a provision for a dose increase up to 1000 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 8 weeks in solid tumor of therapy. Provisions for dose modification were included in the study protocol. Treatment was originally to be continued for 2 years; the protocol was later amended to allow indefinite treatment for patients benefiting from treatment in absence of safety concerns.

The primary objective of the study was to assess the efficacy of imatinib. The B2225 clinical study protocol as well as the published studies did not specifically distinguish between hematologic and cytogenetic response as primary or secondary efficacy end-point, but hematologic response was always used as primary endpoint, at least based upon the temporal evolution of events. Of note, no definition of response was included in the protocol for hematologic malignancies; the activity of imatinib was assessed primarily by evaluating normalization of blood counts and of bone marrow appearance, as well as cytogenetic analysis, FISH analysis for detection of PDGFR rearrangement and PCR analysis for its characterization.

Because these criteria used to asses the peripheral blood and the bone marrow response correspond to the definition of complete hematologic and complete cytogenetic response used in other hematologic malignancies, they are felt adequate to define the therapeutic efficacy of the drug in the disease, and were used in all the case reports published and included in this application.

The defined secondary endpoint in was the ECOG status. No secondary endpoint was specified in the published case reports, although cytogenetic response could be also considered as a secondary endpoint.

Other secondary objectives were to assess the safety and tolerability of imatinib, to evaluate the pharmacokinetic (PK) profile of imatinib in selected patients and to assess, if feasible, the functional significance of relevant signal-transduction components in target tissues by evaluating the expression and activation status of the relevant tyrosine kinase molecules or associated signaling molecules, by measuring indices of cellular proliferation and by correlating the changes in the above findings with clinical outcomes. However, due to the inconsistent collection of biological samples, these latter secondary objectives were not evaluated.

Five to ten patients per indication, condition, or disease were initially enrolled. Lack of clinical efficacy excluded future patients with the same indication, condition or disease from the study. If however, evaluation of the results of the first five patients suggested a positive effect of imatinib by conventional clinical response criteria or other pharmacodynamic measures (e.g. decrease in 18-fluorodeoxyglucose (18-FDG) uptake by positron emission tomography (PET) scanning), additional patients with the same disease could have been enrolled into the study in order to enable adequate evaluation of imatinib effects.

6.1.4 Efficacy Findings

Study B2225 investigators are listed in **Table 6.**

Table 6: B2225 Investigators

Center	Principal Investigator	Study Facility	City, State	Country
101	Prof. Allan Van Oosterom	UZ Gasthuisberg dienst oncologie	Leuven	Belgium
201	Prof. Jane Apperley Prof. John Goldman	Hammersmith Hospitals Dept. of Hematology	London	United Kingdom
301	Dr. Luca Gianni	Istituto Nazionale Tumori	Milano	Italy
401	Dr. Jaap Verweij	Rotterdam Cancer Institute	Rotterdam	Netherlands
501	Dr. George Demetri	Harvard Medical School	Boston, MA	USA
503	Dr. Bart Barlogie	University of Arkansas	Little Rock, AR	USA
504	Dr. Michael Heinrich	Oregon Health Sciences Univ	Portland OR	USA
505	Dr. Robert Shepard	UVA Health System	Charlottesville VA	USA
601	Prof. Heikki Joensuu	Helsinki University Central Hospital	Helsinki	Finland
701	Dr. Denis Soulieres	Centre Hospitalier Universitaire de Montreal	Montreal (Quebec)	Canada
702	Dr. Hal Hirte	Hamilton Regional Cancer Centre McMaster University Medical Centre	Hamilton Ontario	Canada
801	Dr. Richard Herrman	Unikliniken Kantonsspital Basel	Basel	Switzerland
901	Dr. Grant McArthur	Peter MacCallum Cancer Institute	Melbourne	Australia

Demographics, of Study B2225 HES/CEL patients are summarized in **Table 7.**

Table 7: Demographics Characteristics – Study B2225, HES patients

Demographic variable		Total (N = 14)
Sex – n (%)	Male Female	11 (78.6) 3 (21.4)
Race – n (%)	Caucasian Black Oriental	12 (85.7) 1 (8.3) 1 (8.3)
Age (years)	Mean (±SD) Range	48.6 (13.46) 16 – 64

Among the 14 patients with HES in study 2225 there were 4 PR, 2 SD and 6 unknown responses **(Table 8)**.

Table 8: Best overall responses – Study B2225, HES patients

Best response	**n**	**N = 14 %**
Partial response (PR)	4	28.6
Stable disease (SD)	2	14.3
Progressive disease (PD)	2	14.3
Unknown	6	42.9

Response durations for the 4 HES PR's were at least 348, 394, 131 and 183 days and time to progression censored on Days 429, 421, 349 and 210, respectively. Another two patients had SD, one kept on treatment for 678 days while the other progressed after 400 days. Two patients, GBR/201/144 GBR/201/146, had "Unknown" as best response due to missing data; one with time to progression censored on Day 177, the other progressing after 114 days **(Table 9)**. The median duration of therapy was 8.8 months with a range of 16 to 709 days.

Table 9: HES - Best hematologic response and duration

Country/Center/ Subject	Best response	Time to progression (days)	Duration of response
GBR/201/093	PR	349+	131+
GBR/201/144	UNK	114	
GBR/201/145	SD	561+	
GBR/201/146	UNK	177+	
GBR/201/147	UNK	76	
GBR/201/163	SD	400	
GBR/201/178	UNK	99	
CND/701/111	PD	30	
CND/701/169	PD	71	
CND/701/171	PR	210+	183+
AUS/901/120	UNK	16	
AUS/901/152	PR	429+	348+
AUS/901/168	UNK	51	
AUS/901/173	PR	421+	394+

PR = Partial response, SD = Stable disease, UNK = unknown.
* Best response required that responses be accurately coded on two successful visits for confirmation. Otherwise it is listed officially as "Unknown".

Response and response duration of literature HES patients is described in **Table 10** and summarized in **Table 11**.

Of the total population of 176 patients treated for HES/CEL, 107 (61%) achieved a complete hematologic response and 16 (9%) a partial hematologic response (70% overall response rate). Cytogenetic abnormalities were evaluated in 117 of the 176 patients treated in the published reports and in the study B2225. Out of these 117 patients, 61 were positive for FIP1L1-PDGFRα fusion kinase. All these FIP1L1-PDGFRα fusion kinase positive patients achieved a complete hematologic response. The FIP1L1-PDGFRα fusion kinase was either negative or unknown in 115 patients, of which 62 (54%) achieved either a complete (n=46) or partial (n=16) hematologic response.

Table 10: Literature SM Patients-Characteristics, Response and Response Duration

Diagnosis	FIP1L1-PDGFRα fusion gene	Daily Dose (mg/day)	Hematologic response	Duration of response	Cytogenetic response
Single case reports from the published literature†					
19 HES 1 CEL	8 Positive 2 Negative 10 NA	75 to 600	19 Complete 1 Transient*	6 weeks to 18+ months	10 Complete 9 NA
Case series from the published literature					
Gleich, et al (2002): 5 cases a					
HES	NA	100	3 Complete	97+, 105+, 127+ days	NA
			1 None		
Gotlib, et al (2002): 5 cases					
HES	NA	100 to 400	5 Complete	NA	NA
Cools, et al (2003): 11 cases					
HES	5 Positive 5 Negative 1 NA	NA	9 Complete 1 Transient** 1 None	3 (died while in complete remission), 5 (relapse), 3+ (n=2), 7+, 8+, 9+, 11+, 16+ mo	NA
Cortes, et al (2003): 9 cases					
HES	NA	100	4 Complete 1 Transient*** 1 Unknown 3 None	49+ days (n=2)	
Klion, et al (2004): 7 cases					
MP-HES	7 positive	400	7 Complete	1 month (died from unrelated cytomegalovirus infection), 1+ (n=4), 3+ (n=2) months	6 Complete 1 Partial
Pardanani, et al (2003): 5 cases					
HES	NA	100 (n=4) 400 (n=1)	2 Complete 3 Partial b	10+, 14+, 17+, 21+, 33+ weeks	NA
Salem, et al (2003): 6 cases					
HES	NA	100	6 Complete	6+, 12+ (n=2), 19+ (n=2), 22+ wks	NA
Musto, et al (2004): 4 cases					
HES	1 Positive 3 NA	100 (n=1) 400 (n=3))	3 Complete c, d	2, 5 (relapse), 9+ months	1 Complete 3 NA
Payne, et al (2004): 2 cases					
HES	NA	100	1 Complete 1 None	12+ months	NA
Smith, et al (2004): 3 cases					
HES	2 Positive 1 Negative	400 (n=2) 600 (n=1)	3 Complete e	4 (relapse), 7+, 8+ months	NA
Vandenberghe, et al (2004): 5 cases					
CEL	4 Positive 1 Negative	100	4 Complete 1 None	4+ (n=3) months, NA (died of brain hemorrhage)	2 Complete 2 None 1 NA
La Starza, et al (2005): 12 cases f					
6 CEL 5 HES	6 Positive 5 Negative	100 to 600	8 Complete 3 None	2+, 7+, 9+ (n=2), 10+, 11+, 19+, 25+ months	2 Complete 4 None 5 NA

Roche-Lestienne, et al (2005): 9 cases					
6 MP-HES 3 HES	4 Positive 5 Negative		5 Complete 4 None	2+ (=4) mo	NA
Mueller, et al (2006): 2 cases					
HES	1 Positive 1 Negative	100 400	2 complete	16+, 21+ mo	NA
Martinelli, et al (2006): 59 cases					
HES	23 Positive 36 Negative	100 to 400	26 CR, 9 PR, 22 none, 2 NA	1-44 mo	20 complete 2 NA

NA = Not Available; CEL = Chronic Eosinophilic Leukemia; MP = Myeloproliferative

† Schaller and Burkland (2001), Ault, et al (2002), Nolasco, et al (2002), Ishhii, et al (2003), Koury, et al (2003), Ascione, et al (2004), Frickhofen, et al (2004), Malagola, et al (2004), Martinelli, et al (2004), Pottier, et al (2003), Rose, et al (2004), Rotoli, et al (2004), Tan, et al (2004), Wolf, et al (2004), Anghel, et al (2005), Cervetti, et al (2005), Imashuku, et al (2005), Musial, et al (2005), Onitilo, et al (2005), Chung, et al (2006)

* The publication states that the patient presented with a reduction in eosinophils to 10.3% associated with a marked decrease in mast cells after 4 weeks with 100 mg/day imatinib. However, at 8 weeks, the Eo count increased again in the peripheral blood; an increased dose of 200 mg/day was temporarily effective up to 30 weeks of treatment, after which the disease became refractory to the increased dose.

** The publication states that a complete hematologic remission was achieved, although this patient had only a transient response to 100 mg/day imatinib, which lasted several weeks, and had no response to an increased dose of imatinib

*** The publication states that the patient experienced transient normalization of peripheral Eo counts within 1 week of the start of 100 mg/day imatinib. Two weeks later, the symptoms recurred and the Eo count increased without further improvement despite dose increase to 400 mg.

a Including one patient reported by Schaller & Burkland (2001) already counted in the single case reports
b Treatment discontinued in one patient due to CTC grade 3 fatigue
c Duration of response in one patient of 5 months, then relapse
d Treatment discontinued in one patient due to AEs (fatigue, diarrhea, muscle cramps)
e Relapse in one patient with blast crisis
f Including one patient already reported by Rotoli, et al (2003) already counted in the single case reports

Table 11: Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
Positive FIP1L1-PDGFRα fusion kinase	61	61	0
Negative FIP1L1-PDGFRα fusion kinase	56	12	9

Literature HES patients are summarized below:

Schaller and Burkland (2001) were the first to report that treatment with imatinib at a dose of 100 mg/day caused rapid and complete hematologic remission (CHR) in a 41-year-old male patient with HES who suffered from severe, intractable side effects of long-term hydroxyurea and interferon-α therapy.

Ault, et al (2002) reported on a 54-year-old male patient with HES resistant to steroids and chemotherapy, with persistent hip pain. Upon administration of imatinib at 100 mg/day, the patient had a rapid and significant reduction of hip pain, as well as rapid improvement of the hemoglobin and platelet counts and disappearance of eosinophilia. He experienced no apparent side effects during the first 3 months of therapy, but subsequently died from fulminant pneumococcal sepsis.

Gleich, et al (2002) reported positive response to imatinib 100 mg/day in 4 of 5 patients with HES. One of these patients had previously been reported by Schaller & Burkland (2001). They noted hematologic response in 4-7 days with one patient temporarily stopping therapy after 2 weeks due to leukopenia. Responding patients were all males with normal serum interleukin-5 levels. The single patient who did not respond was a female with an elevated (>1100 pg/mL) interleukin-5 level. Analysis for c-Kit activation loop mutation (D816V) in the responding patients was negative, suggesting that c-Kit was not the target of imatinib.

Gotlib, et al (2002) described imatinib treatment of 5 male patients with HES unresponsive to corticosteroids and/or hydroxyurea. The median age of patients was 48 years (range 28-61 years). Four patients had a normal karyotype and one patient had a t(1:4) translocation. All patients were Bcr-Abl negative by cytogenetics or FISH. Imatinib was initiated at doses ranging from 100-400 mg/day. A CHR was rapidly achieved in all patients, which was ongoing at the time of the publication.

Nolasco, et al (2002) reported on a 46-year-old male with normal karyotype and Bcr-Abl negative by PCR analysis. After treatment with interferon-α, coticosteroids and hydroxyurea imatinib at 100 mg/day was started. Within one week, eosinophil (Eo) count decreased rapidly and reached normal levels at the end of the second week of treatment.

Glucocorticosteroids were progressively discontinued and imatinib was tapered to 100 mg twice weekly by the end of the fourth week. A bone marrow biopsy at the time showed only rare Eo's and slight fibrosis. Since then, the patient remains asymptomatic and is off any other type of treatment.

Cools, et al (2003) enrolled 16 patients with HES. All patients had received prior therapy with, but not limited to, prednisone, hydroxyurea and/or interferon-α. Eleven patients (9 men and 2 women) with symptomatic disease (e.g. endomyocardial fibrosis, gastrointestinal Eo infiltrates, cranial nerve palsies, rash, hepatosplenomegaly) were treated with imatinib100-400 mg/day. Treatment resulted in CHR in 10 of 11 patients after a median of 4 weeks (range 1-12 weeks). One of the ten patients had a transient response that lasted several weeks and did not respond to increasing doses of imatinib. The median duration of response in the remaining nine patients was 7 months (range 3-15 months). Analysis of patient DNA for activating mutations in known targets of imatinib (PDGFRα, PDGFβ, c-Kit) indicated the presence of a deletion on 4q12 with a breakpoint near PDGFRα. This deletion left behind fragments of two genes, FIP1L1 and PDGFRα, which fused to form a novel gene, FIP1L1-PDGFRα, which has constitutively active tyrosine kinase analogous to the imatinib sensitive Bcr-Abl enzyme.

Cortes, et al (2003) reported the results of imatinib treatment in 9 patients with HES. All patients had received prior therapy including, but not limited to, steroids, hydroxyurea, interferon-α and/or chemotherapy. All patients were symptomatic at the start of imatinib therapy. The median age was 50 years (range 25-73 years) and 6 patients were men. All patients had normal karyotypes. Four patients achieved CR. All 4 responders were men. All patients in the series were treated with imatinib at 100 mg/day, although in one patient the dose was increased to 400 mg/day before the response could be confirmed.

Ishii, et al (2003) reported one 41-year-old male patient diagnosed with HES and myelofibrosis based on bone marrow biopsy and bronchoalveolar lavage (32% Eo's). He was unsuccessfully treated with prednisolone, interferon-α, hydroxyurea and cyclosporine A. FISH analysis showed no Bcr-Abl fusion. He was started on imatinib at 100 mg/day; after 7 days, absolute Eo count fell to within the normal range and asthma-like symptoms disappeared completely. Imatinib was administered for 7 days at 100 mg/day and then maintained at 100 mg twice weekly. At the time of the publication, no eosinophilia was noted, and there were no notable adverse events.

Klion, et al (2004) analyzed responses in seven HES patients treated with imatinib at 300 to 400 mg/day. Previously, these investigators had found that elevated serum tryptase levels, presence of FIP1L1-PDGFRα, an increase in abnormal mast cells in bone marrow, and tissue fibrosis characterized MP-HES (Klion, et al 2003a). All seven patients had elevated serum tryptase levels and the FIP1L1-PDGFRα mutation in RNA from peripheral blood cells. All seven patients responded to imatinib, achieving CR of symptoms and normalization of Eo levels. Marked symptomatic relief was apparent as early as 3 days after the start of treatment. After 1 mo of imatinib administration, a rapid

and dramatic decrease in Eo was found as well as complete resolution of Eo-related signs, except for cardiac involvement. The lack of reversal of cardiac abnormalities and persistence of the FIP1L1-PDGFRα mutation in one patient suggests that early intervention with higher doses than the administered (300-400 mg/day) of imatinib may be desirable in the treatment of patients with MP-HES. Abnormalities in laboratory test results, including anemia, thrombocytopenia, and elevated serum tryptase and B12 levels resolved in all seven patients. There was also a reversal of BM abnormalities as well as a reduction in aberrant and activated mast cells and activated Eo. The authors concluded that elevated serum tryptase is a sensitive marker of a myeloproliferative variant of HES characterized by tissue fibrosis, poor prognosis, and imatinib responsiveness.

Koury, et al (2003) reported a case where HES was coexisting with a rare skin disease, lymphomatoid papulosis, characterized by multiple transient papular eruptions due to focal dermal T-cell infiltration. A 51-year-old man with HES and lymphomatoid papulosis who had failed treatment with hydroxyurea for HES and methotrexate, psoralen-ultraviolet A light for the skin disorder, presented with severe dyspnea and biventricular heart failure. Serum IL-5 levels were markedly elevated. Imatinib was given at the dose of 400 mg/day for 2 weeks, 200 mg/day for 7 months, and 100 mg/day for 11 months. Eo counts and skin lesions disappeared within a week, serum IL-5 rapidly declined and normalized in 5 weeks; hydroxyurea was discontinued in 2 weeks and prednisone reduced in the course of 6 months. At 6 months, cardiac status improved dramatically and at 18 months the patient was active. The authors concluded that an unidentified TK in the intracellular pathways of IL-5 production or IL-5 receptor signaling is the target for imatinib and that imatinib should be considered for all patients with HES or lymphomatoid papulosis.

Pardanani, et al (2003) treated five HES patients (all male, median age 46 years) and 2 with the very rare eosinophilia-associated chronic myeloid disorder (Eos-CMD) (both male, aged 45 and 58). All patients had failed previous treatments including but not limited to prednisone. At a median follow-up of 17 weeks (range 10-33 weeks), two HES and one eos-CMD patient achieved CHR and one HES achieved PR.

Pottier, et al (2003) published a case report of a 32-year-old male who had hypereosinophilia associated with cutaneous mastocytosis. The patient failed interferon-α and hydroxyurea therapy, but responded completely to imatinib 400 mg/day within three weeks of initiation. The urticaria pigmentosa lesions persisted. The patient was still on therapy after six months.

Salem, et al (2003) reported six patients with idiopathic HES. All patients had received prior therapies including but not limited to corticosteroids alone (n=2) or in association with hydroxyurea (n=2) or with hydroxyurea, interferon-α and cytarabine (n=2). All patients achieved partial response with these initial therapies. Five patients had normal karyotypes and one showed trisomy 8. RT-PCR was negative for ETV6-PDGFRB and

Bcr-Abl fusion mRNAs. All patients rapidly achieved CHR when treated daily with imatinib at 100 mg.

Ascione, et al (2004) reported the case of a 33-year-old man with HES and with cardiac involvement (acute coronary syndrome). A treatment with imatinib at 400 mg/day and warfarin was initiated. After four months, the WBC showed Eo count decreased to normal levels and an ECG revealed normal sinus rhythm without ST segment modifications.

Frickhofen, et al (2004) reported a 33-year-old man with hypereosinophilic syndrome. Treatment with azathioprine and prednisone was started, the patient's condition improved. However, laboratory evaluations confirmed eosinophilia with counts varying between 1.5x109/L (during treatment with azathioprine) and 8.4x109/L (after discontinuation of azathioprine). Cytogenetic analysis revealed a normal karyotype. FISH and RT-PCR analyses revealed no Bcr-Abl translocation. The patient was started on imatinib at 200 mg/day. Within two weeks, Eo count decreased to normal levels and remained there with continued imatinib treatment. At the time of the report, the patient was feeling well without any adverse events.

Malagola, et al (2004) reported the case of a 47-year-old male diagnosed with chronic eosinophilic leukemia (CEL). His karyotype was normal. No Bcr-Abl rearrangement was found, but FIP1L1-PDGFRα rearrangement was detected. Treatment with imatinib was begun on a dose-escalation regimen: 100 mg/day for the first week with weekly dose increases of 100 mg/day up to a maximum dose of 400 mg/day. Seven days after start of treatment, the WBC and eosinophil counts were dramatically reduced and maintained constantly within normal ranges over 120 days of observation. Molecular response was documented 80 days after the start of the treatment.

Martinelli, et al (2004) reported the case of a 65-year-old man presenting with idiopathic HES. RT-PCR analysis detected the FIP1L1-PDGFRα fusion gene but no Bcr-Abl, FGFR1- Bcr or PDGFRα-Tel rearrangement. The patient was started on imatinib at 600 mg/day; after 21 days, the white cell and eosinophils counts fell dramatically and have remained normal over 17 months of continuing treatment.

Musto, et al (2004) observed a t(2:4)(p24:q12) reciprocal translocation in a 64-year-old male affected by HES with complete clinical response, CHR and CCR to imatinib (100 mg/day) sustained for 10 months of follow-up. Cytogenetic and FISH analyses suggested a different molecular abnormality than the FIP1L1-PDGFRα rearrangement. The authors described that while the patient with t(2:4) achieved impressive durable response with 100 mg/day imatinib, for the other three patients 400 to 800 mg/day imatinib was necessary to achieve response.

Payne, et al (2004) reported 2 clinical cases of HES refractory to standard therapy in two male patients with organ involvement. Both were treated with imatinib. In one patient, a

29-year-old man with normal cytogenetics, treatment with imatinib at 100 mg/day produced resolution of symptoms and peripheral blood count within 6 days. The patient had maintained normal blood count s and was symptom free more than one year after start of treatment. The second patient, a 20-year-old man also with normal cytogenetics, failed to respond to imatinib even at a maximum dose of 400 mg/day.

Rose, et al (2004) reported the case of a leukemic form of HES refractory to intensive treatment (including hydroxyurea, prednisone, interferon-α, cytarabine, thiotepa, etoposide and allograft) in whom sustained clinical and molecular response was induced by 200 mg/day imatinib. The 29-year-old male patient in poor clinical status achieved CCR after only 15 days of treatment with imatinib and the response persisted 1 year later.

Rotoli, et al (2004) treated a 37-year-old male affected by Loeffler's endocarditis with imatinib. Cytogenetics, FISH and molecular analyses showed the presence of the FIP1L1-PDGFRα fusion gene. Standard echocardiography revealed a large infiltration of the apical region, with apparently pedunculate corpora floating in the LV chamber. Treatment with imatinib (initially 200 mg/day reduced to 100 mg/day after 2 weeks) caused rapid regression of both eosinophilic proliferation and endomyocardiopathy. Effects were observed after only 2 weeks of treatment with imatinib. The CHR and reversion of the cardiac damage were sustained for 17 months at the time of the report. The FIP1L1-PDGFRα fusion gene was found significantly decreased after a few months of treatment. The authors concluded that imatinib is an excellent candidate for first line treatment of Loeffler's endocarditis, especially when the FIP1L1-PDGFRα fusion gene is detected.

Smith, et al (2004) describe 3 patients with HES with cytogenetic abnormalities (FIP1L1-PDGFRA fusion in two patients, t(5:12)(q33:p13) translocation in a third patient). The two first patients (46- and 52-year-old men) were given imatinib at 400 mg/day and both presented rapid normalization of eosinophils counts; at the time of the publication, they had remained clear for 8 months with no apparent adverse effects from the drug. The third patient, a 56- year-old man, was given imatinib at 600 mg/day; initial rapid resolution of eosinophilia was observed; however, after 4 months of imatinib therapy the patient experienced blast crisis and was administered flavopiridol and depsipeptide.

Tan, et al (2004) describe a 32-year-old male with HES and significant end organ damage who remained refractory to conventional therapy (hydroxyurea). No clonal karyotypic abnormalities were observed. The patient was started on imatinib 100 mg/day. The patient achieved CHR without any side effects reported.

Vandenberghe, et al (2004) retrospectively characterized 17 patients fulfilling WHO criteria for IHES or CEL, using RT-PCR and FISH. Eight patients had FIP1L1-PDGFRα positive CEL, three had FIP1L1-PDGFRα negative CEL and six had IHES. Four FIP1L1-PDGFRα positive patients were treated at an initial dose of 100 mg/day of imatinib. In all four treated patients, including one female, imatinib induced rapid and complete hematologic response with normalization of the peripheral Eo count. Nevertheless, no

clear improvement of the eosinophilic endomyocardial disease was observed in the three patients presenting with cardiac involvement, and one of these patients died from cardiac failure a few weeks later. The presence of FIP1L1-PDGFRα mRNA was analyzed in the blood of the three surviving patients under treatment: the fusion became undetectable by nested PCR in two patients and remained so during 4 months of follow-up. The third sample from the female patient remained positive. In the IHES group of patients, only one patient was treated with imatinib, which was rapidly abandoned for intolerance without evidence of response.

Wolf, et al (2004) describe a 47-year-old man with a HES, diagnosed 20 years ago. The patient was admitted due to insufficient therapeutic response to hydroxyurea: in general, he felt well, but reported increasing neurological problems, such as ataxia, memory deficits and dysarthria. No insertional deletion 4q12 with concomitant fusion of the FIP1L1 to the PDGFRα locus was detected. Magnetic resonance imaging (MRI) indicated a granulomatous vasculitis, most likely due to the hematologic malignancy. Therapy was started with 100 mg/day imatinib. This led to a rapid normalization of eosinophils in the peripheral blood as well as in the bone marrow. Partial cytogenetic remission was achieved at 6 months; CR at 17 months, confirmed at 21 months. Due to the good response at 9 months the dose of imatinib was reduced to 100 mg once weekly, which was subsequently increased at 18 months to 100 mg/day. This led to a rapid normalization of eosinophilic granulocytes in the peripheral blood as well as in the bone marrow. In addition, the neurological symptoms substantially improved.

Anghel, et al (2005) describe the case of a young male patient with a six year history of HES and severe heart involvement who, after unsuccessful treatment attempts with steroids, hydroxyurea and interferon-α, had a prompt, clinical and hematologic complete remission following administration of imatinib. As his cardiac function also markedly improved, he was considered for heart transplant. However, seven years after the onset of the disease and four months after the termination of imatinib treatment the patient died of a cerebral hemorrhage that occurred during an episode of acute respiratory sepsis.

Cervetti, et al (2005) reported on a 61-year-old male presenting with HES and hepatomegaly who was treated with interferon-α for 5 years, obtaining normalization of peripheral blood count with unmodified hepatomegaly. Due to neutropenia, thrombocytopenia, and massive liver and spleen enlargement with appearance of ascites, the treatment was stopped and imatinib at 100 mg/day was initiated. Three months after beginning the treatment, hematologic toxicity resolved and the patient showed significant improvement of hepatomegaly with complete resolution of ascites. The presence of FIP1L1-PDGFRα rearrangement was retrospectively tested on bone marrow samples harvested from the patient at diagnosis and after 12 months of imatinib therapy. The first sample tested positive, whilst the second did not show the FIP1L1-PDGFRα fusion gene.

Imashuku, et al (2005) A 26-year-old man with HES was treated with imatinib following 5 years of prednisolone therapy. The patient had hypereosinophilia (absolute eosinophil count >1500/μL) occurring in cyclic oscillations as well as histologically diagnosed

eosinophilic vasculitis, bursitis, and periodic soft-tissue swellings. Laboratory data revealed high levels of serum tryptase and increased numbers of mast cells in the bone marrow, but serum interleukin-5 levels were within the normal range. The disease initially responded well to 100 mg/day of imatinib but recurred 8 weeks later. Thereafter, a 200 mg/day dose was temporarily effective. Despite the response to imatinib, the FIP1L1-PDGFRα fusion gene was not detected by fluorescence in situ hybridization (FISH) analysis. Additional molecular and cytogenetic studies showed neither translocations of PDGFR genes nor mutations in the c-KIT or the PDGFR genes. Although imatinib appears to be the treatment of choice for patients with HES, its precise molecular mechanism in individual cases remains to be clarified.

La Starza, et al (2005) reported on a multicenter study that included 20 patients fulfilling the WHO criteria for HES and 6 patients without signs or symptoms of end-organ involvement. Ten of the 26 patients presented the FIP1L1-PDGFRα gene. Seven of these 10 patients received imatinib therapy with the peripheral Eo count normalizing within 2-4 weeks. In three patients, interphase FISH and RT-PCR demonstrated cytogenetic and molecular remission during therapy. Five of the FIP1L1-PDGFRα negative patients also received imatinib therapy. Two of these patients achieved hematologic remission with peripheral Eo count normalization.

Musial, et al (2005) reported a 41-year-old man diagnosed with HES with cardiac involvement. Genetic analysis revealed a FIP1L1-PDGFRA fusion gene. The patient was unresponsive to interferon-α therapy. He was started on imatinib at 100 mg/day for the first 3 months and then continued treatment at 100 mg every second day. Full hematologic and molecular remission was accompanied by spectacular improvement in cardiac function.

Onitilo, et al (2005) reported a 50-year-old male patient with HES with trisomy 8 who experienced a complete and durable hematologic and cytogenetic remission with low-dose imatinib therapy (100 mg/day). He also had a significant reversal of cardiac dysfunction with a reduction in cardiac hypertrophy, resolution of pericardial effusion and mitral and tricuspid regurgitation. He remained in remission 3 years after therapy.

Roche-Lestienne, et al (2005) performed molecular characterization of HES in 35 patients with normal karyotypes by conventional cytogenetic analysis. TCRγ gene rearrangements suggesting T clonality were seen in 11 patients (31%), and FIP1L1-PDGFRα by RT-PCR in six of 35 patients (17%), who showed no evidence of T-cell clonality. An elevated serum tryptase level was observed in FIP1L1-PDGFRα-positive patients responding to imatinib, whereas serum IL-5 levels were not elevated in T-cell associated hypereosinophilia. Sequencing FIP1L1-PDGFRα revealed scattered breakpoints in FIP1L1-exons (10-13), whereas breakpoints were restricted to exon 12 of PDGFRα. In the 29 patients without FIP1L1-PDGFRα, no activating mutation of PDGFRα/PDGFRβ was detected; however; one patient responded to imatinib. FISH analysis of the 4q12 deletion was concordant with FIP1L1-PDGFRα RT-PCR data.

Further investigation of the nature of FIP1L1-PDGFRα affected cells will improve the classification of HES. Nine patients were treated with imatinib (100-200 mg/day), seven males, two females, and five of the male HES patients achieved sustained CR.

Chung, et al (2006) reported a case of persistent cough associated with gastro-esophageal reflux and hypereosinophilia. Treatment with proton pump inhibitors and fundoplication did not control the cough. However, high dose prednisolone, but not inhaled corticosteroids, did. The presence of the FIP1L1-PDGFRA fusion gene in myeloid cells was confirmed by fluorescence in situ hybridization analysis using CHIC2 deletion as a surrogate marker. The cough and other disease features were subsequently suppressed by imatinib at the dose of 100 mg/day. This 54 year old male is the first case of persistent cough caused by HES characterized by FIP1L1-PDGFRA fusion gene and aberrant tyrosine kinase activity.

Mueller, et al (2006) summarize recent knowledge of clinical features, pathophysiology and novel treatment aspects of HES by performing a comprehensive search of the available literature and report on 94 patients. The authors particularly address the issue of organ involvement and specific characteristics of the variable clinical pictures. In addition, two cases are presented, which illustrate typical clinical scenarios and treatment outcome.

Martinelli, et al (2006) treated 59 HES patients (age range 18-78) with imatinib. Fifty patients received 100 mg/day increasing by 100 mg/day at weekly intervals to reach the planned dose of 400 mg/day; the imatinib dose was subsequently reduced to 200-300 mg/day in 5 of these patients and maintained at that level due to AEs. Of the remaining nine patients, one patient discontinued before reaching the full dose due to rapid progression and one patient discontinued during dose escalation due to renal failure. One HIV positive patient remained on low dose to prevent possible pharmacological interaction with antiviral therapies. Four patients remained at 100 mg/day per investigator's decision due to concomitant morbidity. The two remaining patients received an unknown dose of imatinib. All patients were studied by molecular analysis for expression of FIP1L1-PDGFRα, Tel-PDGFRβ, FGFR1-Bcr and Bcr-Abl chimerical transcripts. Rapid, hematologic CR was recorded after one month of therapy in all 23 (39%) FIP1L1-PDGFRα positive patients. In 36 patients negative for FIP1L1-PDGFRα rearrangement, 9 (25%) experienced PR and 3 CR (PR+CR 33%). Furthermore, a molecular complete remission (defined as the disappearance of FIP1L1- PDGFRα at qualitative RT-PCR evaluation) was also recorded in 20 FIP1L1-PDGFRα positive patients after 3 months of therapy. The median follow up was 4 months (range 2-39). The authors concluded this study supports the use of imatinib as first line therapy in FIP1L1-PDGFRα positive HES patients.

Secondary efficacy results

The secondary end-point evaluated for efficacy was the ECOG status. The ECOG performance status for the HES population is better at baseline than in the overall

population (no worse than 2). In these patients, the overall ECOG performance status did not change substantially, with two patients having worsened ECOG at the end of the study (but only one with ECOG 2) and two patients improving their ECOG at the end of study from ECOG 1 to ECOG 0 (**Table 12**).

Table 12: ECOG Performance Status

ECOG at baseline		End of study status					
	N	0	1	2	3	4	Missing
0	6	4	1	0	0	0	1
1	4	2	1	1	0	0	0
2	2	0	0	2	0	0	0
Missing	2	1	0	0	0	0	1
Total	14	7	2	3	0	0	2

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

One open-label, multicenter, phase II clinical trial (study B2225) was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. In this study, 14 patients with HES/CEL were treated with 100 mg to 1000 mg of Gleevec daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily. Of the total population of 176 patients treated for HES/CEL, 107 (61%) achieved a complete hematologic response and 16 (9%) a partial hematologic response (70% overall response rate). Cytogenetic abnormalities were evaluated in 117 of the 176 patients treated in the published reports and in study B2225. Out of these 117 patients, 61 were positive for FIP1L1-PDGFRα fusion kinase. All these FIP1L1-PDGFRα fusion kinase positive patients achieved a complete hematologic response. The FIP1L1-PDGFRα fusion kinase was either negative or unknown in 115 patients, of which 62 (54%) achieved either a complete (n=46) or partial (n=16) hematologic response.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology and chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsened after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form only if the patient received study treatment. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy, when they were recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Any Adverse Event occurring after the study completion and within four weeks of last drug intake was recorded on the Adverse Event CRF page.
Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also had to be reported to Novartis within 24-hours of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:
1. is fatal or life-threatening,
2. required or prolonged hospitalization,
3. was significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
Any pregnancy or fathering the child during the study will be considered as an SAE for the purpose of study reporting.

Events not considered serious are hospitalizations occurring under the following circumstances: planned before entry into the clinical study; for elective treatment of a preexisting hospitalization (unless fulfilling the criteria above); routine treatment or monitoring of the study indication and not associated with any deterioration in condition.

Any SAE occurring within four weeks after completion of the study has to be reported and recorded. In addition any pregnancy within 84 days (12 weeks, 3 months) after the last STI571 intake has to be reported and recorded as an SAE.

The institution performed laboratory analyses according to the Visit Schedules.
At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page in addition

to the appropriate laboratory CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

Duration of Gleevec exposure in the 14 HES patients included in study 2225 is summarized in **Table 13** and intensity of exposure is summarized in **Table 14.**

Table 13: Duration of Exposure

Duration of exposure (months)	**HES patients N = 14**
	n (%)
0 – < 5	6 (42.9)
5 – < 10	1 (7.1)
10 – < 15	1 (7.1)
15 – < 20	2 (14.3)
20 – < 25	4 (28.6)
25+	0
Mean ±SD	10.9 ±9.55
Median	8.8
Min – Max	0.5 – 23.3

Table 14: Intensity of Exposure

Absolute dose intensity (mg/day) [1]	**HES patients N = 14**
Mean ±SD	403.0 ±170.07
Median	399.7
Min – Max	109.8 – 743.3

[1] Total dose over the course of the trial/total number of days in trial

Study patient disposition is shown in **Table 15.**

Table 15: Patient Disposition

	HES patients N = 14	
n (%)	**n**	**(%)**
Ongoing at cut-off date	2	(14.3)
Completed	3	(21.4)
Discontinued	9	(64.3)
Unsatisfactory therapeutic effect	8	(57.1)
Adverse events	0	
Subject withdrew consent	1	(7.1)
Death	0	
Condition no longer required study drug	0	
Abnormal laboratory values	0	

AE's in ≥5% of the 14 HES patients are summarized in **Table 16**.

Table 16: Adverse events regardless of study drug relationship

	HES patients N = 14
Preferred term	**n (%)**
Nausea	9 (64.3)
Diarrhea	7 (50.0)
Muscle cramp	7 (50.0)
Periorbital edema	4 (28.6)
Vomiting	4 (28.6)
Bone pain	3 (21.4)
Dyspnea	3 (21.4)
Headache	3 (21.4)
Insomnia	3 (21.4)
Pain in extremity	3 (21.4)
Anemia	2 (14.3)
Asthenia	2 (14.3)
Cough	2 (14.3)
Dry skin	2 (14.3)
Dyspepsia	2 (14.3)
Edema	2 (14.3)
Edema peripheral	2 (14.3)
Eye edema	2 (14.3)
Face edema	2 (14.3)
Loose stools	2 (14.3)
Myalgia	2 (14.3)
Pruritus	2 (14.3)

7.1.1 Deaths

No patient with HES enrolled in Study B2225 died during the study.

There were five deaths reported in patients on treatment with imatinib in the published literature to date:

Ault, et al (2002) reported that their patient developed a fulminant pneumococcal sepsis and expired three months after initiation of treatment with imatinib at 100 mg/day.
Cools, et al (2003) reported that one patient died after 3 months of imatinib treatment while in complete remission, without further detail.
Klion, et al (2004) reported that a patient with endomyocardial fibrosis in whom symptoms and signs of congestive heart failure remained unaffected by imatinib therapy died 1 month after beginning imatinib at 400 mg/day from disseminated cytomegalovirus infection thought to be a result of prolonged high-dose steroid use. At autopsy, extensive endomyocardial fibrosis was evident throughout the ventricular walls and interventricular septum.
Vandenberghe, et al (2004) reported that one patient presenting with cardiac failure and thrombotic events early in his disease course died from cardiac failure a few weeks after starting imatinib at 100 mg/day.
Anghel et al (2005) reported that four months after the withdrawal of imatinib, while in good clinical and hematologic remission, the patient died of a brain hemorrhage that occurred during an episode of acute respiratory sepsis.

7.1.2 Other Serious Adverse Events

Two HES patients experienced three drug-related SAEs: patient [701/111] presented a CTC grade 3 acute renal insufficiency from Day 14 to Day 22 and a CTC grade 3 edema from Day 28 to Day 33, both of which resulted in hospitalization. Patient [901/152] experienced CTC grade 3 decreased sperm count on Day 362 which did not lead to further action.

Three additional HES patients experienced non-related, non-fatal SAEs: patient [201/093] had CTC grade 3 ascites which resolved in two days with non-drug therapy; patient [201/147] had a CTC grade 3 chest infection from Day 7 to Day 20 which led to hospitalization and administration of concomitant medication; he was again hospitalized on Day 24 due to the following SAEs: CTC grade 2 sweating which resolved after one day, CTC grade 2 endomyocardial fibrosis, ischemic lesions in cerebral hemispheres, diarrhea and dizziness and CTC grade 1 nausea, which led to permanent discontinuation of the study treatment. Patient [701/171] had a CTC grade 2 cerebral ischemia from Day 89 to Day 93 which led to hospitalization and the use of concomitant medication.

7.1.3 Dropouts and Other Significant Adverse Events

No study B2225 HES patient withdrew from the study because of AE's. One patient 201/147 developed grade 2 Cerebral ischemia on day 25 that was not suspected of being drug related.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

See **Table 17.**

7.1.6 Laboratory Findings

Hematologic toxicity is shown in **Table 17** and clinical chemistry toxicity is shown in **Table 18.**

Table 17: HES Hematologic Toxicity

Grade	Absolute lymphocytes	Absolute neutrophils	Hgb	Platelets	WBC
Grade 3	N=13 1 (7.7)	N=12 2 (16.7)	N=14 1 (7.1)	N=14 0	N=14 1 (7.1)
Grade 4	0	0	0	0	0

Table 18: HES Clinical Chemistry Toxicity

Grade	Albumin	Alkaline Phosphatase	Creatinine	AST	ALT	Total bilirubin
Grade 3	N=14 1 (7.1)	N=14 0	N=14 1 (7.1)	N=10 0	N=13 0	N=13 0
Grade 4	0	0	0	0	0	0

7.1.7 Vital Signs

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

7.1.8 Electrocardiograms (ECGs)

Disease related ECG changes were reported.

7.1.9 Immunogenicity

There is no new relevant information.

7.1.10 Human Carcinogenicity

There is no new relevant information.

7.1.11 Special Safety Studies

There is no new relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Gleevec has no known potential for abuse..

7.1.13 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 "Sweet's Syndrome" 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

Patients with HES had a median exposure of 156 days (max 393 days).

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 studied.
Doses and durations of exposure were adequate to assess safety for the intended use.
Study design 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

Safety of imatinib has been best evaluated in phase 2 and 3 trials in chronic phase CML. The majority of CML patients experienced drug-related adverse events (AEs) at some time, but most were mild to moderate in severity. Discontinuation for drug related AEs occurred in 2%, of patients in chronic phase CML. 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 Phase III study in 1106 newly diagnosed CML patients Gleevec 400 mg daily was compared to the combination of IFN + Ara-C (study 0106). Gleevec associated myelosuppression was 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. The data indicate that the drug is well tolerated in the target population.

The currently reported AE's in patients with SM are similar to the above known Gleevec adverse effects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Separate safety data was provided for each study. Because of different Gleevec doses, because of the small number of patients studied in each report and because of the large amount of safety data already available it was not felt to be worthwhile to pool safety data. .

7.4.2 Explorations for Predictive Factors

Predictive factors including dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions were not explored in the current study.

7.4.3 Causality Determination

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

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosage of Gleevec® (imatinib mesylate) is 100mg/day to 400 mg/day for adult patients with SM.

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

In accordance with 21 CFR 314.55 the sponsor requests a full waiver of the requirements for submission of data that are adequate to assess the safety and efficacy of Gleevec in

this population of pediatric patients. The basis for this waiver is 314.55c(2)(ii): necessary studies are impossible or highly impractical because the number of patients is so small.

8.5 Advisory Committee Meeting

An ODAC meeting to discuss this application is not planned.

8.6 Literature Review

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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 OVERALL 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

None.

9.3.3 Other Phase 4 Requests

Assure availability of a validated test kit for detection of the FIP1L1-PDGFRα fusion kinase, as determined either directly by mutational analysis or by demonstration of a CHIC2 allele deletion by FISH methodology that implies the presence of the FIP1L1-PDGFRα fusion kinase. The Pre-Market Application (PMA) filing by a 3rd party should occur 3 months after approval.

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.

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Cools J, DeAngelo DJ, Gotlib J, et al (2003) A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med; 348:1201-14.

Cortes J, Ault P, Koller C, et al (2003) Efficacy of imatinib mesylate in the treatment of idiopathic hypereosinophilic syndrome. Blood; 101:4714-6.

Klion AD, Robyn J, Akin C, et al (2004) Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. Blood; 103:473-8.

Musto P, Falcone A, Sanpaolo G, et al (2004) Heterogeneity of response to imatinibmesylate (glivec) in patients with hypereosinophilic syndrome: implications for dosing and pathogenesis. Leuk Lymphoma; 45:1219-22.

Pardanani A, Reeder T, Porrata LF, et al (2003) Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. Blood; 101:3391-7.

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Vandenberghe P, Wlodarska I, Michaux L, et al (2004) Clinical and molecular features of FIP1L1-PDFGRA (+) chronic eosinophilic leukemias. Leukemia; 18:734-42.

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Indicated for ADULT patients with HES?CEL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
ONDQA	21-588

3. NAME AND ADDRESS OF APPLICANT :
Novartis
One Health Plaza
East Hanover, NJ 07936-1080

4. AF NUMBER

5. SUPPLEMENT (S) NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME	SE1-017	3-28-2006
Gleevec	imatinib mesylate		

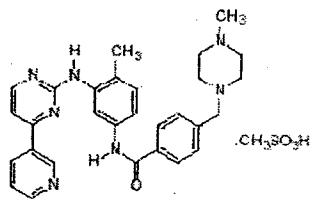
8. SUPPLEMENT PROVIDES FOR: a new indication for the treatment of patients with hypereosinophilic syndrome/chronic eosinophilic syndrome.

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antineoplastic	RX √ OTC	

13. DOSAGE FORM(S)	14. POTENCY
Tablet	100 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE



-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl]benzamide methanesulfonate salt
Molecular Formula: $C_{29}H_{31}N_7O_4$, Molecular Weight: 589.7

16. RECORDS AND REPORTS
CURRENT YES √ NO
REVIEWED YES_NO

17. COMMENTS
In this efficacy supplement 017, the applicant proposed the new indication for the treatment of patients a new indication for the treatment of patients with hypereosinophilic syndrome/chronic eosinophilic syndrome.

There is no CMC change in this supplement.

Novatis has claimed that the drug concentration in all different clinical indications will be below 1 ppb and is qualified for category exclusion from the requirement of environmental assessment per 21 CFR 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended from the standpoints of chemistry, manufacturing and control.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		6-28-2006

DISTRIBUTION		DIVISION FILE	Reviewer: C. Liang	Project Manager:	Branch Chief H. Patelh

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CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
ONDQA	21-588

3. NAME AND ADDRESS OF APPLICANT:	4. AF NUMBER	
Novartis One Health Plaza East Hanover, NJ 07936-1080		5. SUPPLEMENT (S) NUMBER(S) DATES(S)

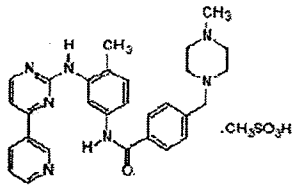
6. NAME OF DRUG	7. NONPROPRIETARY NAME		
Gleevec	imatinib mesylate	SE1-014	2-28-2006

8. SUPPLEMENT PROVIDES FOR: a new indication for the treatment of patients with systemic mastocytosis without the D816V c-kit mutation	9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antineoplastic	RX √ OTC	

13. DOSAGE FORM(S)	14. POTENCY
Tablet	100 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE



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

Molecular Formula: $C_{29}H_{31}N_7O_4$, Molecular Weight: 589.7

16. RECORDS AND REPORTS
CURRENT YES √ NO
REVIEWED YES _ NO

17. COMMENTS

In this efficacy supplement 014, the applicant proposed the new indication for the treatment of patients with systemic mastocytosis without the D816V c-kit mutation.

There is no CMC change in this supplement.

Novatis has claimed that the drug concentration in all different clinical indications will be below 1 ppb and is qualified for category exclusion from the requirement of environmental assessment per 21 CFR 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended from the standpoints of chemistry, manufacturing and control.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		5-22-2006

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CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
ONDQA	21-588

3. NAME AND ADDRESS OF APPLICANT:
Novartis
One Health Plaza
East Hanover, NJ 07936-1080

4. AF NUMBER

5. SUPPLEMENT (S) NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME		
Gleevec	imatinib mesylate	SE1-013 and —	12-21-2005 02-14-2006

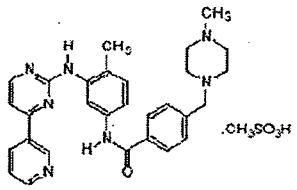
8. SUPPLEMENT PROVIDES FOR:
S-013: Adult patients with Ph+ALL as monotherapy for relapsed and/or refractory patients.

9. AMENDMENTS DATES

b(4)

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antineoplastic	RX √ OTC	
13. DOSAGE FORM(S)	14. POTENCY	
Tablet	100 mg and 400 mg	

15. CHEMICAL NAME AND STRUCTURE



4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl]benzamide methanesulfonate salt
Molecular Formula: $C_{29}H_{31}N_7O_4$, Molecular Weight: 589.7

16. RECORDS AND REPORTS
CURRENT YES √ NO
REVIEWED YES _ NO

17. COMMENTS
In efficacy supplement 013, the applicant proposed the new indication for the treatment of patients with Philadephia chromosome (Ph+) chronic myeloid leukemia and with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

b(4)

There is no CMC change in this supplement.

Novatis has claimed that the drug concentration in all different clinical indications will be below 1 ppb and is qualified for category exclusion from the requirement of environmental assessment per 21 CFR 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended from the standpoints of chemistry, manufacturing and control.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		3-22-2006

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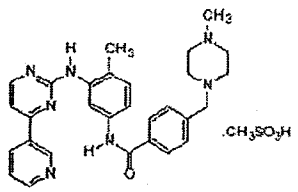
CHEMIST'S REVIEW

	1. ORGANIZATION ONDQA	2. NDA NUMBER 21-588
3. NAME AND ADDRESS OF APPLICANT: Novartis One Health Plaza East Hanover, NJ 07936-1080		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Gleevec	7. NONPROPRIETARY NAME imatinib mesylate	SE1-011/012 12-19-2005
8. SUPPLEMENT PROVIDES FOR: the new indication for the treatment of adult patients with unresectable recurrent metastatic dermatofibrosarcoma protuberans.		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Tablet	14. POTENCY 100 mg and 400 mg	
15. CHEMICAL NAME AND STRUCTURE  4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl]benzamide methanesulfonate salt Molecular Formula: $C_{29}H_{31}N_7O_4$ Molecular Weight: 589.7		16. RECORDS AND REPORTS CURRENT YES √ NO REVIEWED YES NO

17. COMMENTS

In this efficacy supplement, the applicant proposed the new indication for the treatment of adult patients with unresectable recurrent metastatic dermatofibrosarcoma protuberans.

There is no CMC change in this supplement.

Novatis has claimed that the drug concentration in all different clinical indications will be below 1 ppb and is qualified for category exclusion from the requirement of environmental assessment per 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended from the standpoints of chemistry, manufacturing and control.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		2-28-2006

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APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-588
Submission Date	011: December 16, 2005 012: December 19, 2005 013/015: December 20, 2005 014: February 28, 2006 017: March 28, 2006
Brand Name	Gleevec®
Generic Name	imatinib mesylate
Formulation	100 and 400 mg tablets
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Brian Booth, Ph.D.
OCPB Division	Division of Clinical Pharmacology V
ORM Division	Division of Drug Oncology Products
Sponsor	Novartis Pharmaceuticals
Submission Type; Code	Supplemental NDA; 011, 012, 013, 014 & 017
Indication	011: Dermatofibrosarcoma protuberans (DFSP) 012: Myelodysplastic/proliferative disorder (MDS/MPD) 013: As monotherapy in patients with relapsed or refractory Philadelphia chromosome positive ALL b(4) 014: Systemic Mastocytosis (SM) 017: Hypereosinophilic syndrome (HES)
Dosing regimen	DFSP: 800 mg/day MDS/MPD: 400 mg/day Ph+ ALL: 600 mg/day SM: 100 or 400 mg/day HES: 100 or 400 mg/day

An Optional Inter-division briefing was held on September 21, 2006

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FIGURE 2: Mean plasma concentration-time profiles of CGP74588 on Day 1 (n=21) and Day 29 (n=11) following once daily administration of Gleevec 400 mg 10

1 Executive Summary

This review evaluates the pharmacokinetic results obtained in study B2225 which was submitted as a supplemental NDA in support of obtaining approval for four new indications.

Background

Gleevec (imatinib mesylate) is approved for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy, for the treatment of newly diagnosed patients with Philadelphia 2 chromosome positive (Ph+) CML in chronic phase, and for the treatment of patients with Kit (CD117) positive metastatic and/or unresectable malignant gastrointestinal stromal tumors (GIST). The recommended adult dosage of Gleevec is 400 mg/day in chronic phase CML, 600 mg/day in accelerated CML phase or blast crisis, and 400 mg/day or 600 mg/day in unresectable and/or metastatic, malignant GIST.

In the present sNDA submission, the Applicant is requesting approval for additional indications for Gleevec which were submitted as separate sNDAs as follows:

- Supplement 011: for treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)
- Supplement 012: for treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor gene re-arrangements.
- Supplement 013 [redacted] as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL (013). b(4)
- Supplement 014: for the treatment of patients with systemic mastocytosis (SM) without the D816V c-kit mutation.
- Supplement 017: for the treatment of patients with hypereosinophilic syndrome (HES)

As noted above each supplement was submitted separately. Only one study which included multiple disease states was conducted to support the indications for supplements 011, 012, 014 and 017.

- CSTI571B2225: An open-label, pilot phase 2 study of ST1571 in patients with life threatening diseases known to be associated with one or more ST1571-sensitive tyrosine kinases.

For the Ph+ ALL indication three clinical reports were submitted and were reviewed by the medical division. No new studies were completed, however data from newly diagnosed patients and Ph+ALL patients was extracted from previous studies/reports to support the new indication. All of these studies have been previously reviewed and no new pharmacokinetic data was submitted.

- CSTI571 I 03 001: A phase 1, dose-finding study to determine the safety, tolerability and PK/PD profiles, and to evaluate for preliminary anti-leukemic

effects of STI571 in patients with CML resistant to interferon (only a pediatric patient (i.e., newly diagnosed patients) addendum was submitted)

- CSTI571 I 0109 - A phase 2 study to determine the safety and anti-leukemic effects of STI571 in adult patients with Ph+ ALL, AML, CML lymphoid blast crisis and accelerated CML. (Population PK submitted and reviewed with original application)
- CSTI571 I 0114 - An expanded access protocol of STI571 in adult patients with either CML in accelerated phase or Ph+ ALL (no PK taken in the trial)

1.1 Recommendations

The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated. There were no labeling changes relevant to Clinical Pharmacology proposed by the sponsor.

Reviewer: Julie M. Bullock, Pharm.D. Division of Clinical Pharmacology 5	Acting Team Leader: Brian Booth, Ph.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **A Staten;** MTL - **J Johnson**; MO - **M Cohen**
DCP-5: Reviewer - **J Bullock;** TL - **B Booth;** DD - **A Rahman**

2 Clinical Pharmacology Summary

Detailed clinical pharmacology and biopharmaceutics information has been previously submitted and reviewed in the original NDA 21-335 (submission of 27-Feb-2001) and NDA 21-588 (submission of 13-Dec-2002)

In the present submission, the sponsor submitted a Phase 2 study (B2225) which investigated the use of Gleevec in rare diseases. The primary objective of the study was to assess the efficacy of imatinib in patients with life threatening diseases known to be associated with one or more of the known imatinib-sensitive tyrosine kinases following failure of standard therapeutic options. One of the secondary objectives in this study was to evaluate the pharmacokinetic profile of imatinib in selected patients.

A subset of patients underwent intensive pharmacokinetic sampling on Day 1 and Day 29 and sparse sampling was taken in other patients as deemed convenient. The pharmacokinetic results in this patient population of rare diseases did not differ from the pharmacokinetic results concluded in previous reviews in patients with GIST or CML.

3 Question Based Review

Imatinib has been reviewed previously under NDA 21-335 for CML (submission of 27-Feb-2001) and GIST (submission of 15-October-2001). NDA 21-588 has the same indications, but is for the tablet formulation instead of the capsule formulation used in NDA 21-335. For brevity only QBR questions regarding this current supplemental NDA submission will be addressed below. For additional information please see posted clinical pharmacology reviews in DFS.

3.1 General Clinical Pharmacology

3.1.1 What are the design features of the pivotal clinical studies?

Study B2224 was an open label, multi-center, phase II clinical trial testing imatinib in patients with life threatening diseases known to be associated with Abl, Kit or PDGFR protein tyrosine kinases (PTK's). One hundred and eighty five patients suffering from 37 different malignances were recruited into the study over a 47-month period. The following table shows the number of patients suffering from each of the 13 different malignances which were assessed for efficacy and safety

TABLE 1: Breakdown of solid tumors and hematological malignancies that were studied in protocol B2224

Group	Diagnosis	n (%)
Solid Tumors	Adenoid cystic carcinoma	12 (6.5)
	Aggressive fibromatosis	20(10.8)
	Chondrosarcoma	7(3.8)
	Chordoma	4 (2.2)
	Dermatofibrosarcoma protuberans	12 (6.5)
	Leiomyosarcoma	11 (5.9)
	Liposarcoma	11 (5.9)
	Mesothelioma	6 (3.2)
	Synovial sarcoma	16 (8.6)
Hematological malignancies	Hypereosinophilic syndrome	14 (7.6)

	Mastocytosis	5 (2.7)
	Myelofibrosis	8 (4.3)
	Myelodysplastic/proliferative disorder	7 (3.8)

Patients with hematological malignancies were to receive imatinib initially at 400 mg PO daily with doses being increased up to 800 mg PO daily if no significant improvement in the disease occurred after the first 4-8 weeks on therapy. Patients with solid tumors were to receive imatinib initially at 800mg PO daily (400 mg bid) with doses being increased up to 1000 mg PO daily if no significant improvement in the disease occurred after the first eight weeks on therapy.

The primary objective of study B2225 was to assess the efficacy of imatinib in patients with life threatening diseases known to be associated with one or more of the known imatinib-sensitive tyrosine kinases, following failure of standard therapeutic options. The efficacy criteria varied according to the disease being treated. Patients with solid tumors were assessed by means of computerized tomography or magnetic resonance imaging scanning. The hematological malignancies were assessed using blood counts and bone marrow analyses.

Response was assessed using the Southwestern Oncology Group (SWOG) criteria. A complete response (CR) was defined as a complete disappearance of all measurable and evaluable disease. A partial response (PR) was defined as greater than or equal to 50% decrease in tumor size for solid tumors or for collections of abnormal cells in the bone marrow.

Of the 13 diseases with evaluable results, four conditions yielded results with evidence of efficacy of imatinib treatment (see Table 2).

TABLE 2: Summary of the response results in hematological malignancies and DFSP

Disease type	Best response	n (%)
Hematological Malignancies		
Hypereosinophilic syndrome (N=14)		6 (50.0)
	Partial response (PR)	4 (28.6)
	Stable disease (SD)	2 (14.3)
	Progressive disease (PD)	2 (14.3)
	Unknown*	6 (42.9)
Mastocytosis (N=5)	Partial response (PR)	1 (20.0)
	Stable disease (SD)	1 (20.0)
	Unknown*	3 (60.0)
Myeloproliferative disorder (N=7)	Complete response (CR)	3 (42.9)
	Partial response (PR)	1 (14.3)
	Progressive disease (PD)	1 (14.3)
	Unknown*	2 (28.6)
Solid Tumors Malignancies		
DFSP (N=12)	Complete response (CR)	1 (8.3)
	Partial response (PR)	8 (66.7)
	Unknown*	3 (25.0)

3.1.2 What is the basis for selecting the response endpoints or biomarkers and how were they measured in the clinical study?

Primary evidence of activity in any disease or condition was recorded as the investigators evaluation of a patient's tumor response at each visit where response was assessed. When

possible, the status of tumor lesions in patients with solid tumors was assessed by means of CT or MRI. For patients with skin lesions with DFSP, the lesions were evaluated for surface area, depth, thickness and consistency of the lesions. Hematological malignancies were assessed using blood counts and bone marrow analyses.

Tissue samples were collected when possible and analyzed for possible functional significance of one or more of the relevant imatinib-sensitive PTK's. This data was not provided in the study report.

3.1.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma concentrations for pharmacokinetics were assessed after single and multiple doses by high-performance liquid chromatography MS/MS method (LC/MS/MS). The assay method for Gleevec has been previously reviewed and accepted.

Blood samples for the measurement of the plasma profiles of imatinib and its metabolites (major metabolite CGP74588) were collected from a selected patient population. Full profiles were taken from patients when concomitant medication was known or suspected to interact with imatinib, for patients with liver impairment, and for patients with metabolic, absorption or excretion disorders. On Day 1 samples were taken at predose, 1, 2, 3, 8, and 24, 48 and 72 hours. On Day 29 samples were taken at 1, 2, 3, 8, and 24 hours.

Sparse sampling on Day 1 and Day 29 was implemented for all other patients. Briefly, 3 samples were taken between 1hr and 3hr, between 6hr and 9hr after drug intake, and before taking the capsule the following day.

3.1.4 Exposure Response

Due to the small number of patients in each group, a meaningful dose response relationship could not be discerned. The breakdown of the doses given to patients with malignancies showing efficacy and the corresponding number of patients with responses are listed in Table 3 below. There was little benefit to higher doses in the hematological malignancy group as those receiving 800 mg/day did not have higher rates of response than those receiving 400 mg/day. For the solid tumor malignances, only two patients received doses other than 800 mg/day therefore a comparison could not be made.

TABLE 3: DFSP dose at time of Best Response

Dose (n)	CR	PR	SD	PD	Unknown
Solid Tumor Malignancy					
DSFP (12)					
400 mg (1)		1			
600 mg (1)					1
800 mg (10)	1	7			2
Hematological Malignancy					
HES (14)					
100 mg (2)		1	1		
400 mg (10)		2	1	1	6
600 mg (2)		1		1	
SM (5)					
100 mg (1)					1

400 mg (4)		1	1		2
MDS/MPD (7)					
400 mg (5)	2	1		1	1
800 mg (1)					1
1000mg (1)	1				

CR= Complete Response
PR = Partial Response
SD = Stable Disease
PD = Progressive Disease

Below is the breakdown of dose intensity of the diseases evaluable for efficacy (Table 4).

TABLE 4: Dose intensity by main disease type in the hematological and solid tumor malignancy groups.

Disease type	Absolute dose intensity (mg/day)
Hematological Malignancy Group	
Hypereosinophilic syndrome (N=14)	
Mean ± SD	403 ± 170.07
Median	399.7
Min - Max	109.8 - 743.3
Mastocytosis (N=5)	
Mean ± SD	214.2 ± 169.49
Median	155.9
Min - Max	19.6 - 393.2
Myeloproliferative disorder (N=7)	
Mean ± SD	433.1 ± 275.36
Median	395.7
Min - Max	50.8 - 880.5
Solid Tumor Group	
DFSP (N=12)	
Mean ± SD	741.2 ± 122.98
Median	799.7
Min – Max	400 - 800

Only one dose reduction, and no dose increases, were recorded for the DFSP group. The doses of one patient were decreased from 800 mg/day to 600 mg/day on Day 10, and they remained on 600 mg/day until Day 21 when the patient stopped treatment (response was unknown). There were more dose increase/decreases in the hematological malignancies with 15 out of the 26 patients requiring dose adjustments. On occasion the dose was increased, however there was no trend seen with increasing doses and increasing response rates. One patient went from 400 mg/day to 100 mg/day in the HES group and completed the study (503 days) with a partial response. One patient in the Myeloproliferative disorder group was titrated up to 1000 mg/day on Day 337 and achieved a complete response on Day 421. This patient remained at 1000 mg/day until Day 812.

The median duration of exposure to imatinib was 6.2 months for DFSP, while the other solid tumor malignancies had median exposures that ranged from 0.9 to 5.5 months. Patients in the hematological malignancy group had lower median doses and higher durations of exposure (8.8 to 13 months), with 7 patients continuing on therapy for 20-25 months.

There were more Grade 3 AE's recorded for the solid tumor group (61) than in the hematological group (21) which correlates with the higher doses which were given to the solid tumor group. Of note, GI SAE's were more frequent in patients with hematological

malignancies while respiratory SAE's were more frequent in the solid tumor patients.

3.1.5 Pharmacokinetic Characteristics

What are the single dose and multiple dose PK parameters?

Pharmacokinetic data in study B2225 were collected at different dose levels from 200 mg to 800 mg per day following the first dose and at steady state on Day 29. Twenty-seven patients participated in intensive PK sampling on Day 1 and 18 had PK drawn on Day 29. Sparse samples were also taken in 64 patients on Day 1 and in 30 patients on Day 29. The breakdown of patients who participated in the PK sampling and their type of malignancy was not provided by the sponsor.

The majority of the intensive pharmacokinetic data is from the 400 mg QD dose (Table 5). Gleevec accumulated approximately 1.5 fold which is consistent with previous results for this compound. The active metabolite, CGP74588 showed a greater accumulation of two to three fold, and a longer half-life than the parent compound, which has been noted in previous reviews of Gleevec pharmacokinetics. At steady-state, the parent to metabolite exposure ratio is approximately 5 fold. The plasma concentrations of imatinib and the metabolite in these patients (Figures 1 & 2) are consistent with those observed in patients with CML or GIST. A correlation between PK differences and the 13 different indications studied was not made due to the limited availability of data.

TABLE 5: Summary of pharmacokinetic parameters of imatinib on Day 1 and Day 29

Dose (mg/day)	Parameter (units)	Day 1	Day 29
200	N	3	3
	AUC(0-24) (ng.h/mL)	25927(4058)	38016(8394)
	AUC(0-∞) (ng.h/mL)	34780(1672)	NA
	Cmax (ng/mL)	2500(266)	2387(729)
	tmax (h)	2[1-2.1]	1.9[1-3]
	t½ (h)	14.0(6.3)	NA
300	N	1	2
	AUC(0-24) (ng.h/mL)	47353	33603-159136
	AUC(0-∞) (ng.h/mL)	64798	NA
	Cmax (ng/mL)	3490	1880-9230
	tmax (h)	3	3-3.3
	t½ (h)	14.3	NA
400	N	21	11
	AUC(0-24) (ng.h/mL)	56011(30174)	75223(22356)
	AUC(0-∞) (ng.h/mL)	102295(65194)	NA
	Cmax (ng/mL)	3447(1523)	4207(1342)
	tmax (h)	3[2-72]	3[1-22.9]
	t½ (h)	16.4(3.5)	NA
800	N	2	2
	AUC(0-24) (ng.h/mL)	33155-71032	12038-55480
	AUC(0-∞) (ng.h/mL)	57716-156143	NA
	Cmax (ng/mL)	2800-3630	1190-3660
	tmax (h)	3	2-3
	t½ (h)	12.6-24-7	NA

FIGURE 1: Mean plasma concentration-time profiles of imatinib mesylate on day 1 (n = 21) and Day 29 (n=11) following once daily administration of Gleevec 400 mg.

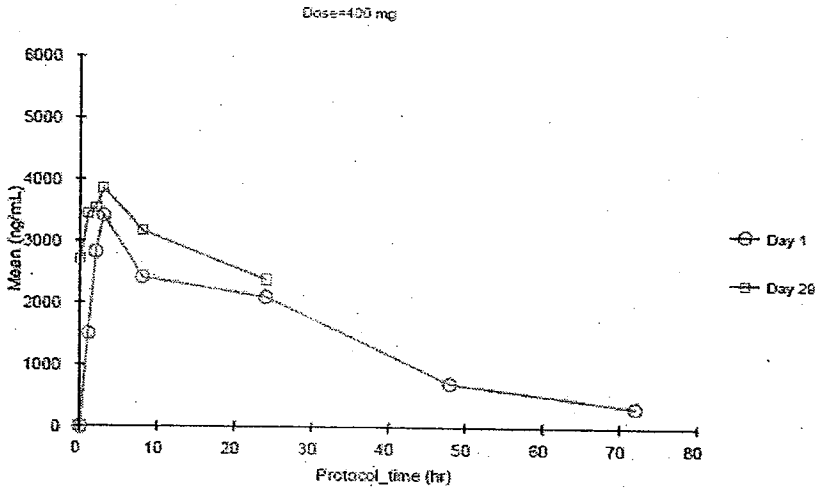
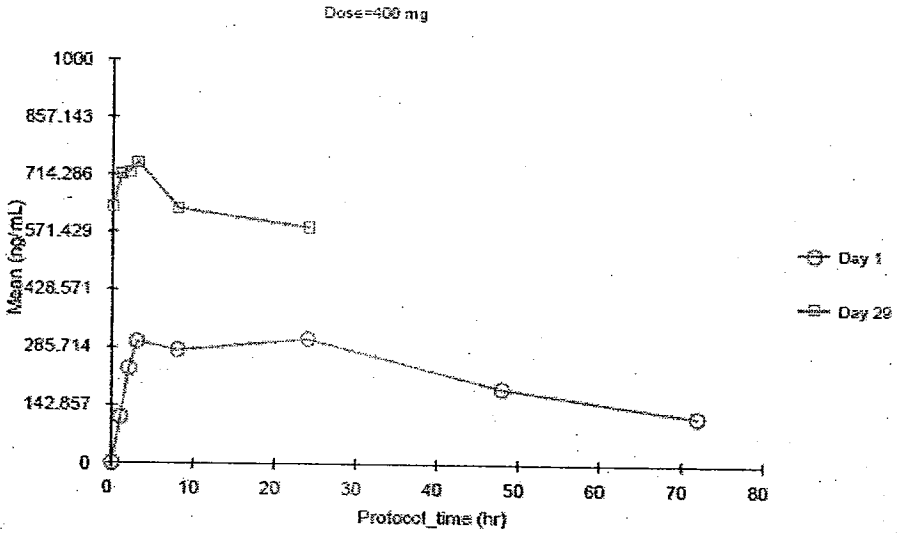


FIGURE 2: Mean plasma concentration-time profiles of CGP74588 on Day 1 (n=21) and Day 29 (n=11) following once daily administration of Gleevec 400 mg



The trough concentration results from sparse sampling are provided in Table 6. These results are similar to results seen in patients with CML and GIST. At the 600 mg dose, the trough concentrations were similar to that in GIST patients (see study 2222) who had troughs reported as 2141 ng/mL after dosing with 600 mg. In patients with CML at steady state the 400 mg and 800 mg trough concentrations from previous studies were 1216 ng/mL and 2660 ng/mL respectively.

TABLE 6: Summary of trough plasma concentrations (Mean ± SD) of imatinib on Day 1 and Day 29 following 400, 600 and 800 mg doses in patients.

Dose (mg/day)	Time (hr)	Day 1 ng/mL (mean±SD)[N]	Day 29 ng/mL (mean ± SD)[N]	Day 29 to Day 1 ratio
400	24 hr	894± 1126 [14]	1430± 588 [5]	1.6

600	24 hr	2070 [1]	2420± 1399 [4]	NA
800	24 hr	1953± 1242 [49]	2766± 1751 [21]	1.4

3.2 Intrinsic Factors

No information in this study report was provided for the patients who underwent pharmacokinetic analysis regarding the age, gender, race, weight, height, or disease.

3.3 Extrinsic Factors

No information regarding extrinsic factors and their influence on dose and exposure/response were provided in this study report.

4 Detailed Labeling Recommendations

No changes by the sponsor were proposed to the label pertaining to clinical pharmacology. Only the relevant clinical pharmacology sections are included below.

Highlights indicate information that the sponsor added, or ~~removed~~ from the current approved labeling. Double underlines indicate content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.

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 Cmax 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-1,000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 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 α1-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. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar to that of the parent compound.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-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 Cmax of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m2 in children vs. 10.0 L/hr/m2 in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Dosing in children at both 260 mg/m2 and 340 mg/m2 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/m2 and 340 mg/m2 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: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

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 Cmax 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 Cmax 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 = 3.5- to 4.3-fold), which represents mean decreases in Cmax, AUC(0-24) and AUC(0-∞) 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 Ki 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.)

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PRECAUTIONS

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 Cmax and AUC(0-∞). 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 Cmax 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.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (Ki value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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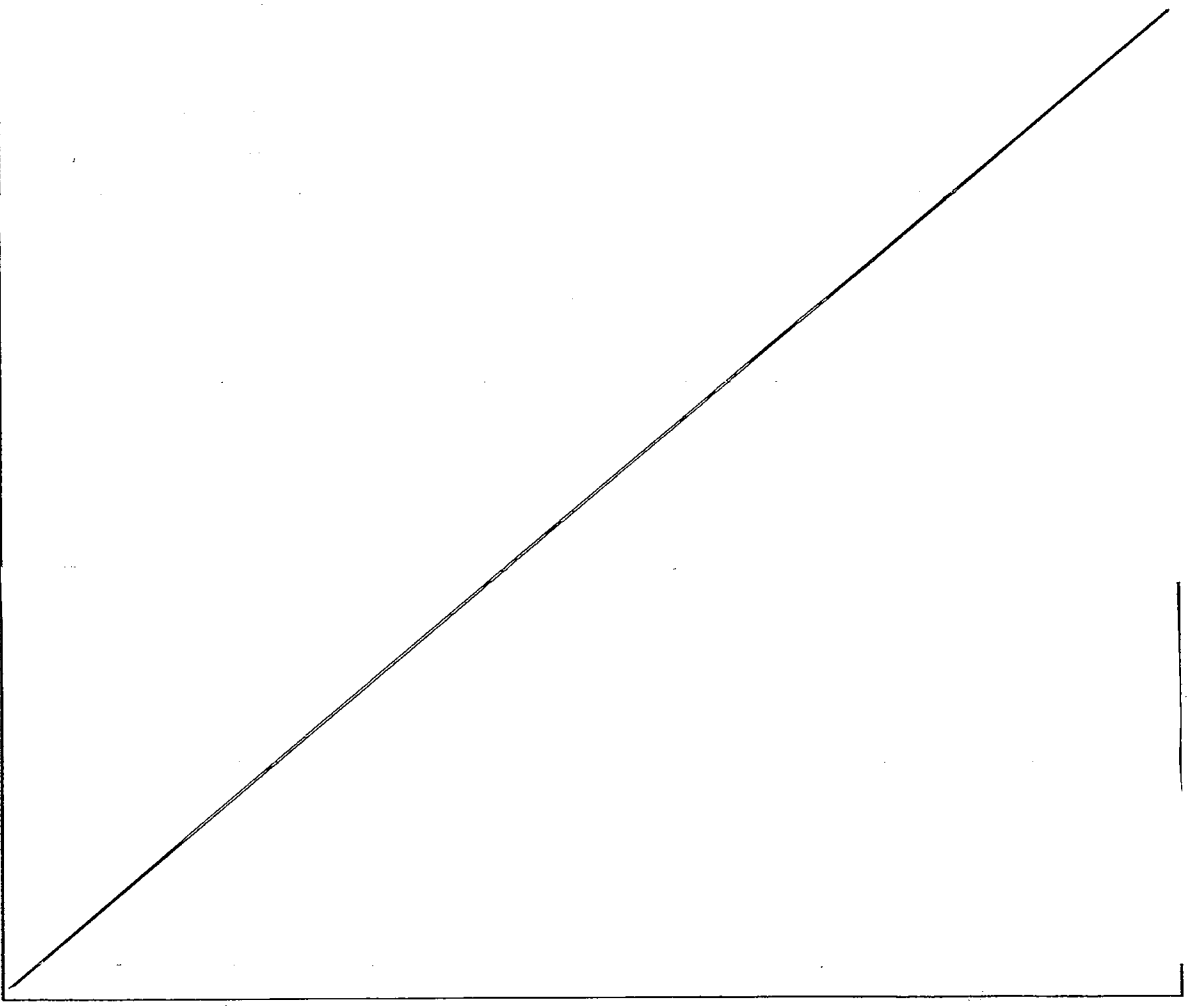
DOSAGE AND ADMINISTRATION



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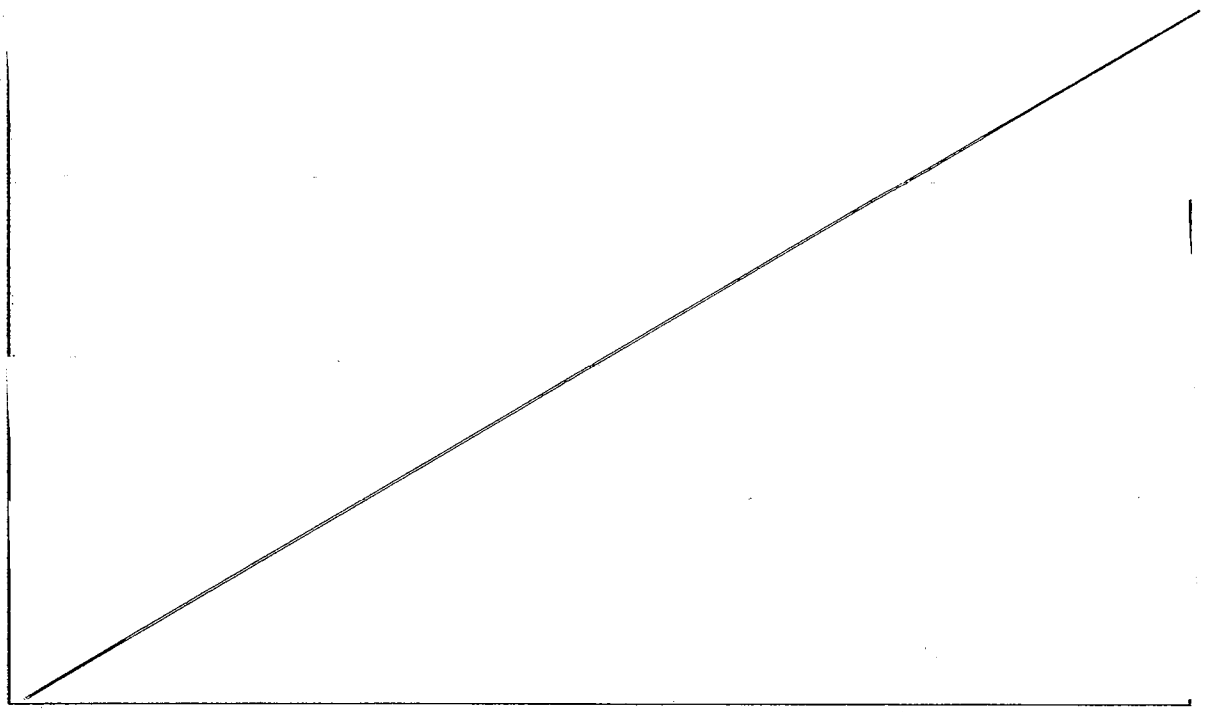

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5 Appendices

5.1 Referenced reviews

5.1.1 Original NDA 21-335 - CML

Submitted on Feb 27, 2001, April 10, 2001 and April 12, 2001. Review completed and posted by John Duan, Ph.D. in DFS.

5.1.2 sNDA 21-335 - GIST

Submitted on Oct 15, 2001 and Dec 7, 2001. Review completed and posted by Gene Williams, PhD. in DFS

5.1.3 Original NDA 21-588 switch from capsules to tablets

Submitted on December 13, 2002. Review completed and posted by Anne Zajicek, M.D., Pharm.D. in DFS

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

/s/

Julie Bullock
9/21/2006 10:09:37 AM
BIOPHARMACEUTICS

Brian Booth
9/21/2006 10:16:56 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

OTHER REVIEW(S)

Division of Drug Marketing, Advertisement, and Communications

Enforcement Branch II

Internal Consult

****Pre-decisional Agency Information****

To: Martin Cohen, MD, Medical Officer, DODP

From: Joseph A. Grillo, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

CC: Ann Staten, Project Manager, DODP

Date: May 16, 2006

Re: NDA # 21-588
MACMIS # 14188
Gleevec® (Imatinib mesylate) Tablets
Comments on draft Labeling

In response to your revised consult request via email on May 10, 2006, we have reviewed the draft Labeling for the -011, -012, -013, -014, — -017 NDA supplements and offer the following comments:

Section	Statement from draft	Comment
CLINICAL PHARMACOLOGY Mechanism of Action	[redacted]	Please add additional context regarding whether this claim is based on *in vitro* or *in vivo* data.

b(4)

Section	Statement from draft	Comment
CLINICAL STUDIES Newly diagnosed Ph+ ALL		The "relapsed/refractory" section does the same. Because the new indications clearly state that should it be clarified for the reader why these distinctions were made? The current presentation of the results is somewhat confusing.
CLINICAL STUDIES Newly diagnosed Ph+ ALL		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted.
CLINICAL STUDIES Newly diagnosed Ph+ ALL		Does this information regarding secondary endpoints represent substantial evidence? If not it should be omitted.

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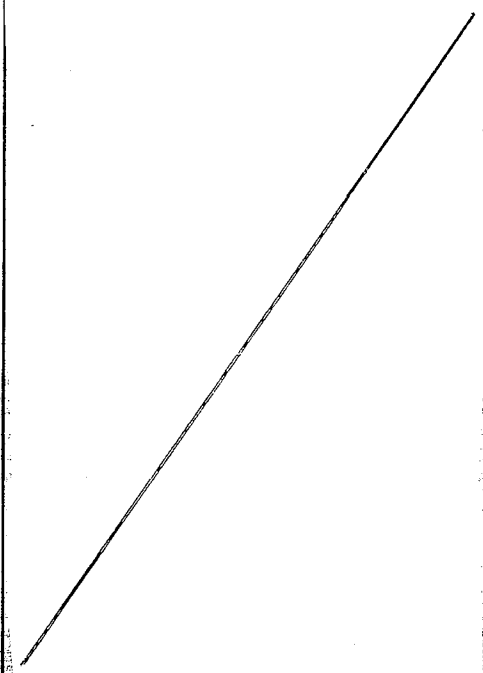
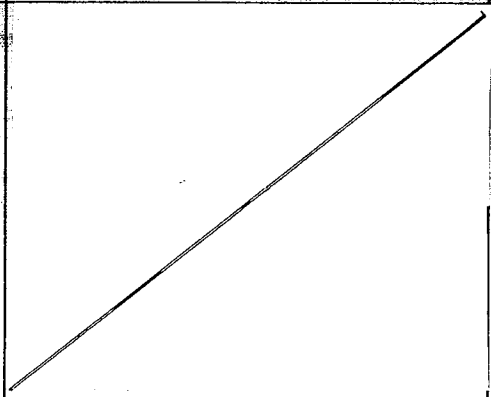
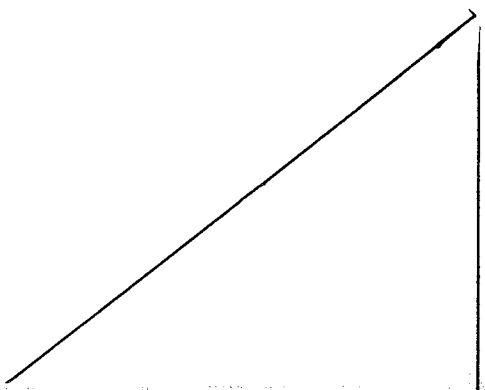
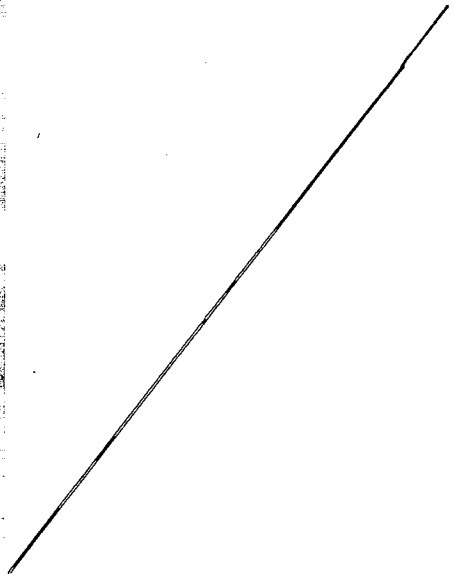
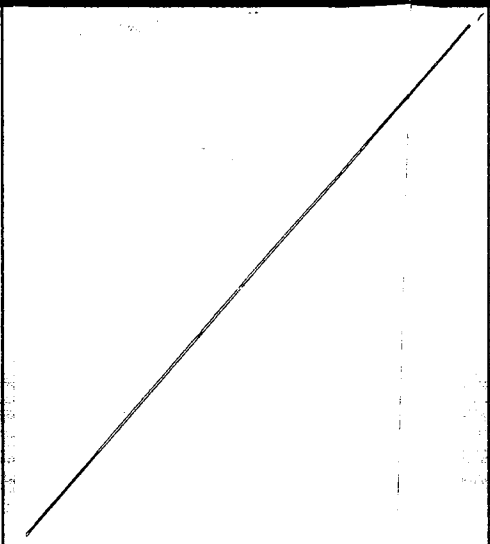
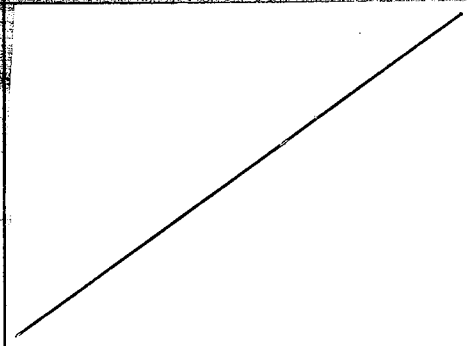
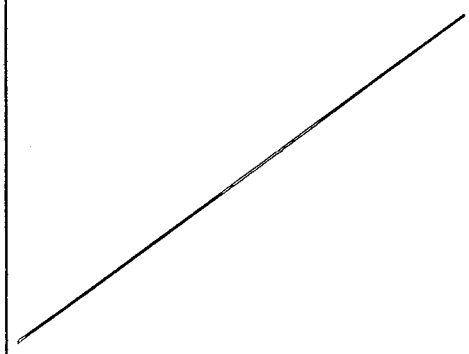
Section	Statement from draft	Comment
CLINICAL STUDIES Newly diagnosed Ph+ ALL		This comparison will be used promotionally. Is this a valid comparison? If not it should be omitted
CLINICAL STUDIES ~~Newly diagnosed Ph+ ALL~~	Table 4	Does this information regarding secondary endpoints represent substantial evidence? If not it should be omitted.
CLINICAL STUDIES Relapsed/refractory Ph+ ALL		Does this information regarding secondary endpoints represent substantial evidence? If not it should be omitted.

b(4)

b(4)

Section	Statement from draft	Comment
CLINICAL STUDIES Relapsed/refractory Ph+ ALL		Does this information regarding This subgroup analysis represent substantial evidence? If not it should be omitted. b(4)
CLINICAL STUDIES Myelodysplastic/ Myeloproliferative diseases		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted. b(4)
CLINICAL STUDIES Myelodysplastic/ Myeloproliferative diseases	"Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within ——— and ranged between 1 week and more than 18 months in responding patients in the published literature."	This will be used promotionally to imply a survival benefit. If this presentation does not represent substantial evidence it should be omitted. b(4)

Section	Statement from draft	Comment
CLINICAL STUDIES Systemic Mastocytosis		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted.
CLINICAL STUDIES Systemic Mastocytosis		This will be used promotionally to imply a survival benefit. If this presentation does not represent substantial evidence it should be omitted.
CLINICAL STUDIES Hypereosinophilic Syndrome / Chronic Eosinophilia		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted.
CLINICAL STUDIES Hypereosinophilic Syndrome / Chronic Eosinophilia		Does this information represent substantial evidence? If not it should be omitted.

b(4)

b(4)

b(4)

b(4

Section	Statement from draft	Comment
CLINICAL STUDIES Dermatofibrosarcoma Protuberans	"Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of them completely (37%). "	This presentation will be used promotionally to suggest a greater response than was observed in Table 5. If this presentation does not represent substantial evidence it should be omitted.
CLINICAL STUDIES Dermatofibrosarcoma Protuberans	"The median duration of therapy in study ——— was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months."	This will be used promotionally to imply a survival benefit. If this presentation does not represent substantial evidence it should be omitted.
INDICATIONS	[redacted]	If this is to be approved under Subpart H please add standard language regarding the lack of a clinical benefit.

b(4)

b(4)

Section	Statement from draft	Comment
PRECAUTIONS General	[redacted]	This may be used promotionally to minimize the risk of Gleevec in this population. Does this recommendation represent substantial evidence? Could additional contextual information be added? [redacted] b(4) ." If this is not correct, we suggest this paragraph have its own subheading or be set off in another manner to avoid confusion.
PRECAUTIONS General ADVERSE REACTIONS Hepatotoxicity	[redacted]	The term [redacted] will be used promotionally to minimize risk. It should be omitted unless there is substantial experience that this is true. b(4) Are any dose adjustments or interruptions required in this setting?
ADVERSE REACTIONS ALL	[redacted]	Terms such as "mild," "easily manageable," "rarely severe," and "may be managed..." are promotional will be used to minimize the risk associated with Gleevec. They should be omitted if possible. b(4)

Section	Statement from draft	Comment
ADVERSE EVENTS	Table 14 &17	As is recommended in the newly finalized guidance on the Adverse Reactions section of labeling, the adverse events should be listed in descending order of frequency in the table. They currently appear in an apparently random order.
ADVERSE EVENTS Hypereosinophilic Syndrome / Chronic Eosinophilia	[redacted]	The term [redacted] " is promotional will be used to minimize the risk associated with Gleevec. It should be omitted if possible.
DOSAGE AND ADMINISTRATION		For ease of reading as the list of indications for Gleevec grows, we recommend that the dosing information be presented in bulleted format, rather than in the current paragraph format.

b(4)

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/s/

Joseph Grillo
5/16/2006 01:35:26 PM
DDMAC REVIEWER

Division of Drug Marketing, Advertisement, and Communications

Enforcement Branch II

Internal Consult

****Pre-decisional Agency Information****

To: Martin Cohen, MD, Medical Officer, DODP

From: Joseph A. Grillo, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

CC: Ann Staten, Project Manager, DODP

Date: April 17, 2006

Re: NDA # 21-588
MACMIS # 14188
Gleevec® (imatinib mesylate) Tablets
Comments on draft Labeling

In response to your consult request via email on January 6, 2006, we have reviewed the draft Labeling for the -011, -012, and -013 NDA supplements and offer the following comments:

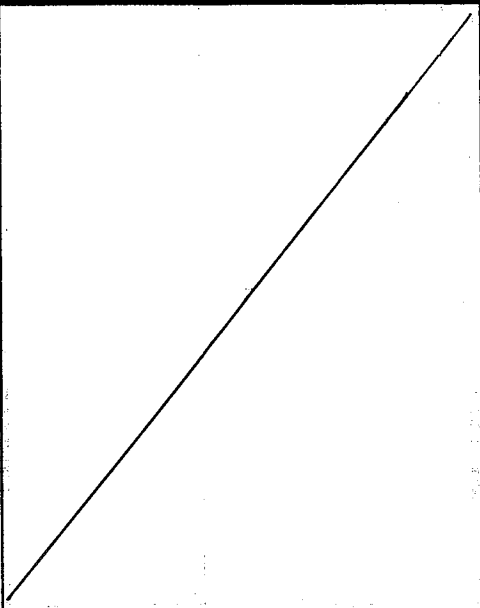
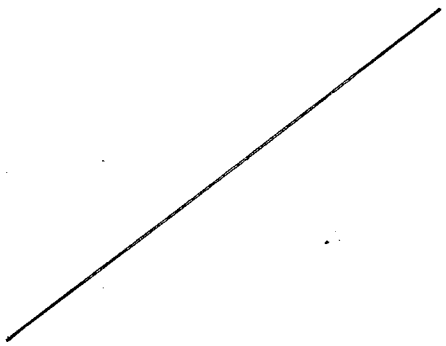
21-588-011

Section	Statement from draft	Comment
CLINICAL STUDIES Dermatofibrosarcoma Protuberans	"Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of them completely (37%). "	This presentation will be used promotionally to suggest a greater response than was observed in Table 5. If this presentation does not represent substantial evidence it should be omitted.

Section	Statement from draft	Comment
CLINICAL STUDIES Dermatofibrosarcoma Protuberans	[redacted]	This will be used promotionally to imply a survival benefit. If this presentation does not represent substantial evidence it should be omitted. b(4)
CLINICAL STUDIES Dermatofibrosarcoma Protuberans	[redacted]	Because the proposed indication is for adult patients with DFSP, results in the pediatric patient are understandably not discussed under Clinical Studies. Should the outcome in the lone pediatric patient be discussed elsewhere in the label, e.g., in the Precautions-Pediatric Use section?
INDICATIONS	[redacted] adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP). [redacted] Dermatofibrosarcoma Protuberans.)"	If this is to be approved under Subpart H please add standard language regarding the lack of a clinical benefit. b(4)
ADVERSE EVENTS	Table 12	As is recommended in the newly finalized guidance on the Adverse Reactions section of labeling, the adverse events should be listed in descending order of frequency in the table. They currently appear in an apparently random order.
DOSAGE AND ADMINISTRATION		For ease of reading as the list of indications for Gleevec grows, we recommend that the dosing information be presented in bulleted format, rather than in the current paragraph format.

21-588-012

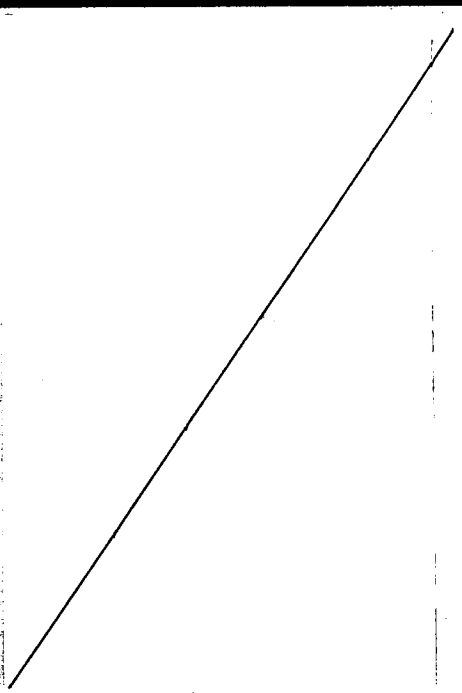
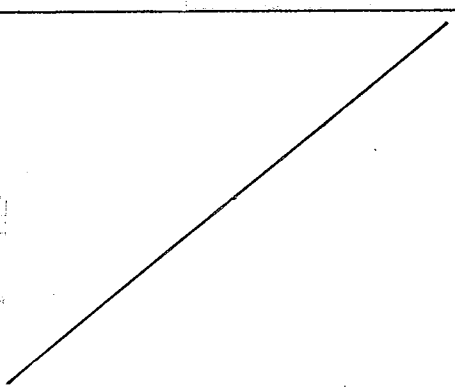
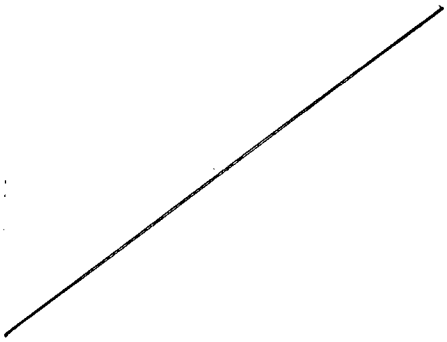
Section	Statement from draft	Comment
CLINICAL PHARMACOLOGY Mechanism of Action	[redacted]	Please add additional context regarding whether this claim is based on *in vitro* or *in vivo* data. b(4)

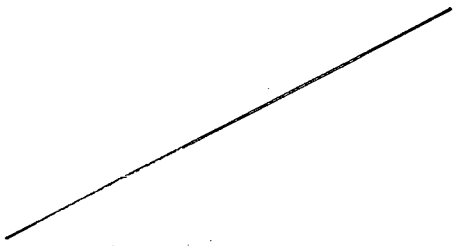
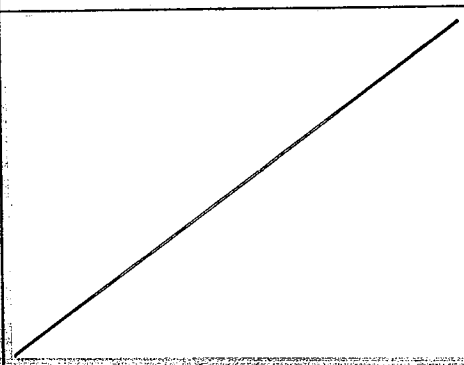
Section	Statement from draft	Comment
CLINICAL STUDIES Myelodysplastic/ Myeloproliferative diseases		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted. b(4)
CLINICAL STUDIES Myelodysplastic/ Myeloproliferative diseases	"Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within ——— and ranged between 1 week and more than 18 months in responding patients in the published literature."	This will be used promotionally to imply a survival benefit. If this presentation does not represent substantial evidence it should be omitted. b(4)
INDICATIONS	——— treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements"	If this is to be approved under Subpart H please add standard language regarding the lack of a clinical benefit. b(4)
PRECAUTIONS General		This may be used promotionally to minimize the risk of Gleevec in this population. Does this recommendation represent substantial evidence? Could additional contextual information be added? As proposed, this new paragraph seems to belong under the subheading for the section that precedes it, "Fluid Retention and Edema." If this is not correct, we suggest this paragraph have its own subheading or be set off in another manner to avoid confusion. b(4)
ADVERSE REACTIONS – MDS/MPD	Table 10	As noted for S-011, adverse events should be listed in decreasing order of frequency in the table.

Section	Statement from draft	Comment
DOSAGE AND ADMINISTRATION		As noted for S-011, we recommend using bullets to present the recommended doses for the multiple indications.

21-588-013

Section	Statement from draft	Comment
CLINICAL STUDIES Newly diagnosed Ph+ ALL		The "newly diagnosed" section discusses Gleevec use ——— ——— The "relapsed/refractory" section does the same. Because the new indications clearly state that newly diagnosed patients should get ——— and relapsed/refractory patients should get Gleevec ———should it be clarified for the reader why these distinctions were made? The current presentation of the results is somewhat confusing. b(4)
CLINICAL STUDIES Newly diagnosed Ph+ ALL		Please add additional context regarding whether this claim is based on *in vitro* or *in vivo* data. b(4)
CLINICAL STUDIES Newly diagnosed Ph+ ALL		This subgroup analysis will be used promotionally to suggest a greater response in this subpopulation. If this presentation does not represent substantial evidence it should be omitted. b(4)
CLINICAL STUDIES Newly diagnosed Ph+ ALL		Does this information regarding secondary endpoints represent substantial evidence? If not it should be omitted. b(4)

Section	Statement from draft	Comment
CLINICAL STUDIES Newly diagnosed Ph+ ALL		This comparison will be used promotionally. Is this a valid comparison? If not it should be omitted b(4)
CLINICAL STUDIES Relapsed/refractory Ph+ ALL		Does this information regarding secondary endpoints represent substantial evidence? If not it should be omitted. b(4)
CLINICAL STUDIES Relapsed/refractory Ph+ ALL		Does this information regarding This subgroup analysis represent substantial evidence? If not it should be omitted. b(4)

Section	Statement from draft	Comment
INDICATIONS		If this is to be approved under Subpart H please add standard language regarding the lack of a clinical benefit. b(4)
PRECAUTIONS General ADVERSE REACTIONS Hepatotoxicity		The term '[redacted]' will be used promotionally to minimize risk. It should be omitted unless there is substantial experience that this is true. Are any dose adjustments or interruptions required in this setting? b(4)
ADVERSE REACTIONS ALL	"The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported drug-related adverse events reported in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec."	Terms such as "mild," "easily manageable," "rarely severe," and "may be managed..." are promotional will be used to minimize the risk associated with Gleevec. They should be omitted if possible.
DOSAGE AND ADMINISTRATION		As noted for S-011 and S-012, we recommend using bullets to present the recommended doses for the multiple indications.

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/s/

Joseph Grillo
4/18/2006 10:15:53 AM
DDMAC REVIEWER

PROJECT MANAGER REVIEW OF LABELING

NDA 21-588/S-011; 012; 013; 014; 017

Drug:	**Gleevec (imatinib mesylate) Tablets, 100 and 400 mg**
Applicant:	**Novartis Pharmaceutical Corporation**
Submission Dates:	**December 16, 19 and 20, 2005; January 24, February 28, March 28, April 10, May 15, 18 and 24, 2006**
Receipt Date:	**December 19 and 21, 2005; January 26, March 1, 29, April 11, May 17, 19 and 25, 2006**

BACKGROUND:

On December 20, 2004, Novartis submitted an efficacy supplement (S-008) to provide for changes to the package insert to reflect additional data accumulated from ongoing studies in GIST, new dose escalation data in newly diagnosed Ph+ CML and data from one of the phase 4 commitments. This supplement 008 was approved on October 20, 2005.

On December 7, 2005, Novartis submitted FPL (FA) for S-008 which also contained a new "Changes Being Effected" (CBE) supplement (S-010). S-010 adds new precautionary and adverse reaction information to the package insert

On December 13, 2005, Novartis submitted labeling to replace the December 7, 2005 package insert after discovering a typographical error in the December 7, 2005 version.

On December 19, 2005, Novartis submitted two efficacy supplements (S-011 and S-012) for the following indications:

> S-011: For the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
>
> S-012: For the treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.

On December 21, 2005, Novartis submitted an efficacy supplement (S-013) for the treatment of adult patients with relapsed or refractory Ph+ ALL.

On March 1, 2006, Novartis submitted an efficacy supplement (S-014) for the treatment of patients with Systemic Mastocytosis (SM) without the D816V c-kit mutation.

Finally, on March 29, 2006, Novartis submitted an efficacy supplement (S-017) for the treatment of patients with hypereosinophilic syndrome (HES).

Supplement 010 was approved on May 31, 2006.

DOCUMENTS REVIEWED:

I compared the text for the FPL submitted December 13, 2005 (S-010) to the proposed text for the package insert submitted May 15 (S-011 and S-012), 18 (S-013 and S-014) and 24 (S-017), 2006.

REVIEW:

The only changes in the new version are those the sponsor proposes for this supplement.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The proposed draft package insert text submitted on April 10, 2006 with tracked changes is attached.

With the concurrence of the Medical and Clinical Pharmacology reviewers in their individual reviews, this labeling may be approved (see their reviews).

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

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

38 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

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/s/

Ann Staten
6/7/2006 07:41:27 AM
CSO

Dotti Pease
6/7/2006 03:13:10 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-588 / S-011, 012, 013, 014, 017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-335 and 21-588

NAME OF APPLICANT / NDA HOLDER
Novartis Pharmaceuticals Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Gleevec

ACTIVE INGREDIENT(S)	STRENGTH(S)
Imatinib mesylate	50mg and 100 mg capsules 100 mg and 400 mg tablets

DOSAGE FORM
Capsules and tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,521,184	1/16/2004	1/4/2015

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novartis Pharmaceuticals Corporation	One Health Plaza	
	City/State East Hanover, New Jersey	
	ZIP Code 07936	FAX Number *(if available)* (973) 781-5217
	Telephone Number (862) 778-0233	E-Mail Address *(if available)* joseph.quintavalla@novartis.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☒ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

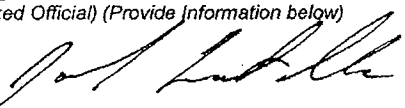
	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	9/16/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Joseph Quintavalla, Ph.D.	
Address One Health Plaza (105\PL040)	City/State East Hanover, NJ
ZIP Code 07936	Telephone Number 1-862-778-0233
FAX Number *(if available)* 1-973-781-5217	E-Mail Address *(if available)* joseph.quintavalla@novartis.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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

PSC Media Arts (301) 443-1090 EF

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-335 and 21-588

NAME OF APPLICANT / NDA HOLDER
Novartis Pharma AG

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Gleevec

ACTIVE INGREDIENT(S)	STRENGTH(S)
Imatinib mesylate	50mg and 100 mg capsules 100 mg and 400 mg tablets

DOSAGE FORM
Capsules and tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,894,051	5/17/2005	5/23/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novartis Pharma AG	Lichtstrasse 35	
	City/State CH-4056, Basel, Sitzerland	
	ZIP Code 07936	FAX Number *(if available)*
	Telephone Number (011)416-1324	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	One Health Plaza	
	City/State East Hanover, NJ	
	ZIP Code 07936	FAX Number *(if available)* 1-973-781-5217
	Telephone Number 1-862-778-0233	E-Mail Address *(if available)* joseph.quintavalla@novartis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☒ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

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6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/16/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Joseph Quintavalla, Ph.D.	
Address One Health Plaza (105\PL040)	City/State East Hanover, NJ
ZIP Code 07936	Telephone Number 1-862-778-0233
FAX Number *(if available)* 1-973-781-5217	E-Mail Address *(if available)* joseph.quintavalla@novartis.com

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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PSC Media Arts (301) 443-1090 EF

NOVARTIS

1.3.6 Patent Certification – 505(b)(2)

This submission for the indication of systemic mastocytosis relies in part on data described in research publications, and therefore filed as a 505(b)(2) application. Pursuant with CFR 314.50 i(1)ii, Novartis is the sole owner of Gleevec patents, and there are no patents in our application claiming the use of Gleevec for the treatment of any of the New Indications that would be infringed upon.

Certification:

In the opinion and to the best knowledge of Novartis Pharmaceuticals Corporation, there are no patents, other that those belonging to Novartis, that claim the drug on which investigations that are relied upon in this application were conducted or that claim a use of such drug for the treatment of any of the New Indications.

2/10/06

Joseph Quintavalla, PhD Senior Regulatory Manager	Date

NOVARTIS

1.3.6 Patent Certification – 505(b)(2)

This submission for the indication of dermatofibrosarcoma protuberans (S-011) for NDA 21-588, relies in part on data described in research publications, and therefore filed as a 505(b)(2) application. Pursuant with CFR 314.50 i(1)ii, Novartis is the sole owner of Gleevec patents, and there are no patents in our application claiming the use of Gleevec for the treatment of any of the New Indications that would be infringed upon.

Certification:

In the opinion and to the best knowledge of Novartis Pharmaceuticals Corporation, there are no patents, other that those belonging to Novartis, that claim the drug on which investigations that are relied upon in this application were conducted or that claim a use of such drug for the treatment of any of the New Indications.

6/26/06

Joseph Quintavalla, PhD Senior Regulatory Manager	Date

NOVARTIS

1.3.6 Patent Certification – 505(b)(2)

This submission for the indication of recurrent or refractory Ph+ acute lymphoblastic anemia (Ph+ ALL) (S-013) for NDA 21-588, relies in part on data described in research publications, and therefore filed as a 505(b)(2) application. Pursuant with CFR 314.50 i(1)ii, Novartis is the sole owner of Gleevec patents, and there are no patents in our application claiming the use of Gleevec for the treatment of any of the New Indications that would be infringed upon.

Certification:

In the opinion and to the best knowledge of Novartis Pharmaceuticals Corporation, there are no patents, other that those belonging to Novartis, that claim the drug on which investigations that are relied upon in this application were conducted or that claim a use of such drug for the treatment of any of the New Indications.

6/26/06

Joseph Quintavalla, PhD Senior Regulatory Manager	Date

NOVARTIS

1.3.6 Patent Certification – 505(b)(2)

This submission for the indication of hypereosinophilic syndrome (HES) (S-017) for NDA 21-588, relies in part on data described in research publications, and therefore filed as a 505(b)(2) application. Pursuant with CFR 314.50 i(1)ii, Novartis is the sole owner of Gleevec patents, and there are no patents in our application claiming the use of Gleevec for the treatment of any of the New Indications that would be infringed upon.

Certification:

In the opinion and to the best knowledge of Novartis Pharmaceuticals Corporation, there are no patents, other that those belonging to Novartis, that claim the drug on which investigations that are relied upon in this application were conducted or that claim a use of such drug for the treatment of any of the New Indications.

6/20/06

Joseph Quintavalla, PhD Senior Regulatory Manager	Date

EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 011 HFD # 150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 10-19-06

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

SE1

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 - this is incorrect, but I believe Novartis is confused because this is an orphan indication

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?

NO

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:

B2225

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:

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:

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"):

B2225

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: Dotti Pease
Title: CPMS
Date: 10-12-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, DDOP

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/

Robert Justice
10/20/2006 06:26:37 PM

EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 012 HFD # 150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 10-19-06

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

SE1

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 - this is incorrect, but I believe Novartis is confused because this is an orphan indication

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?

NO

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:

B2225

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:

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:

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"):

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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: Dotti Pease
Title: CPMS
Date: 10-12-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, DDOP

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/

Robert Justice
10/20/2006 06:30:25 PM

EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 013 HFD # 3150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 10-19-06

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

SE1

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 - this is incorrect, but I believe Novartis is confused because this is an orphan indication

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?

NO

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:

03001
0109
0114

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:

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:

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"):

03001
0109
0114

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 # 55,666 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: Dotti Pease
Title: CPMS
Date: 10-12-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, DDOP

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

/s/

Robert Justice
10/20/2006 06:37:29 PM

EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 014 HFD # 150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 10-19-06

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

SE1

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 - this is incorrect, but I believe Novartis is confused because this is an orphan indication

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?

NO

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:

B2225

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:

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:

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"):

B2225

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: Dotti Pease
Title: CPMS
Date: 10-12-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, DDOP

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/

Robert Justice
10/20/2006 06:41:25 PM

EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 017 HFD # 150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 10-19-06

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

SE1

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 - this is incorrect, but I believe Novartis is confused because this is an orphan indication

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?

NO

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:

B2225

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:

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:

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"):

B2225

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: Dotti Pease
Title: CPMS
Date: 10-12-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, DDOP

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/

Robert Justice
10/20/2006 06:46:04 PM

NOVARTIS

NDA No. 21-588

Gleevec®
(imatinib mesylate)
tablets
New Drug Application

NOVARTIS CERTIFICATION IN COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Joseph Quintavalla, Ph.D.
Senior Manager
Drug Regulatory Affairs

9/2/05
Date: September 2, 2005

Pease, Dorothy W

From: Cohen, Martin H
Sent: Monday, October 16, 2006 9:58 AM
To: Pease, Dorothy W; Cohen, Martin H; Johnson, John R; Justice, Robert
Subject: RE: Gleevec PMCs for the multiple indications

John and Dotti,

I think that we should retain our original aggressive systemic mastocytosis indication with its' qualifiers so as to prevent confusion.

While I am not totally happy I think that we can accept MDS/MPD rather than MDP/MDS.

Marty

From: Pease, Dorothy W
Sent: Monday, October 16, 2006 6:58 AM
To: Cohen, Martin H; Johnson, John R; Justice, Robert
Subject: FW: Gleevec PMCs for the multiple indications

Novartis proposed revisions in multiple indications labeling.

Dotti

From: jeremy.brace@novartis.com [mailto:jeremy.brace@novartis.com]
Sent: Friday, October 13, 2006 1:53 PM
To: Pease, Dorothy W
Cc: robert.miranda@novartis.com; joseph.quintavalla@novartis.com
Subject: Re: Gleevec PMCs for the multiple indications

Dear Dotti,

Further to your e-mail below and that of October 10 in which you provided a draft label for these supplements we have now had a chance to review the proposed label and have a few comments and suggestions. Overall the label is acceptable but we would like the Agency to consider the attached changes. I have detailed below the rationale for our changes and have provided a clean copy of the label with our proposed revisions.

- Myelodysplastic/Myeloproliferative diseases (MDS/MPD) is the WHO designated classification for these disorders(see attached publication). We wish to maintain consistency with this WHO classification and propose reverting back to this description throughout the label. If the Agency disagree then can you please provide us with an understanding of why the term Myeloproliferative/Myelodysplastic diseases (MPD/MDS) is preferred.
- In the section on Clinical Studies for DFSP (starting line 379 in the attached revised label) the correct terminology to describe the gene rearrangement is the PDGF B gene. Use of the beta symbol is in relation to the PDGF receptor. Hence this has been corrected in lines 382,393 and 401.
- We propose to simplify the wording for the indication for ASM so that it describes the patient population where Gleevec should be used, consistent with the other indications (line 441). We agree that the information on those forms of SM where Gleevec has not shown to be effective and is not

approved is important information and we have included this in the Clinical Studies section for ASM (line 359).

- We consider all of the information in the Precautions section to be important to prescribers and have reorganised this section into a logical and more organised order based on alphabetical description of the title. This approach is consistent with that taken in the previously approved PIs.

In addition to this we would like to suggest that we reorganise the Indications section to make this section easier to read as per the attached. If the Agency agrees I can provide a revised label to include this.

With regard to postmarketing commitments I can confirm that Novartis accept the PMCs as detailed in your e-mail below.

I hope that the proposed changes and suggestions are acceptable and that we can finalise these approvals as soon as possible.

Just to let you know that I will be at the RAPS Annual Conference in Baltimore from Monday 16th to Wednesday 18th but I will have access to emails and telephone. However, please ensure that you copy in Bob Miranda and Joe Quintavalla on any correspondence for Gleevec in my absence.

Thanks and kind regards

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
Drug Regulatory Affairs
Novartis Oncology
Building 105/2E075
East Hanover, NJ 07936, USA
Phone: +1 862-778-2942
Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

10/13/2006 10:03 AM

To: jeremy.brace@novartis.com
cc: robert.miranda@novartis.com
Subject: Gleevec PMCs for the multiple indications

Please see below for the FDA team's revisions to your postmarketing commitments for S012, S014, and S017:

1. (for S012) To meet with the Division and the FDA Center for Devices and Radiological Health (CDRH) Office of In Vitro Diagnostics within 3 months to discuss the feasibility of a ———— validated test kit for PDGFR gene rearrangements for patients with MPD/MDS. b(4)
2. (for S014) To meet with the Division and the FDA CDRH Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the

10/16/2006

development of a validated test kit for the detection of the D816v c-kit mutation in aggressive systemic mastocytosis.

3. (for S017) To meet with the Division and FDA CDRH Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the development of a validated test kit for the detection of the FIP 1L1-PDGFR-alpha fusion protein in HES/CEL.

Any update on the labeling?

We are on track at this end to get the letter out on time or a day or two ahead of time, depending on Novartis' response to labeling and PMCs.

The letter for —— due next Friday, and I hope to make that date also. b(4)

Thanks

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

10/16/2006

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT
NOVARTIS PHARMACEUTICALS CORPORATION

DATE OF SUBMISSION
September 26, 2006

TELEPHONE NO. *(Include Area Code)*
(862) 778-2942

FACSIMILE (FAX) Number *(Include Area Code)*
973-781-5217

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

One Health Plaza
East Hanover, New Jersey 07936-1080

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: **21-588**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
imatinib mesylate

PROPRIETARY NAME *(trade name)* IF ANY:
Gleevec/Glivec

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

CODE NAME *(If any)*:
STI571

DOSAGE FORM:
Tablet

STRENGTHS:
100 mg and 400 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:
CML and GIST

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☒ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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

REASON FOR SUBMISSION
Efficacy Supplements

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

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION *(Full establishment information should be provided in the body of the Application.)*

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

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

IND 55,666 NDA 21-588 NDA 21-335

PSC Media Arts (301) 443-1090 EF

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

CERTIFICATION

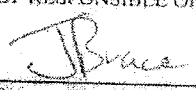
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
☒ 	Jeremy Brace, Senior Associate Director Drug Regulatory Affairs	9/26/06

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(862) 778-2942

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

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

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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

Pease, Dorothy W

From: jeremy.brace@novartis.com
Sent: Tuesday, September 26, 2006 2:24 PM
To: Pease, Dorothy W
Cc: joseph.quintavalla@novartis.com; robert.miranda@novartis.com
Subject: RE: Gleevec pending supplements
Attachments: 20060926 Efficacy Supplement.pdf

Dear Dotti,

Further to your e-mail please find attached the formal submission of our response to the proposed postmarketing commitments for supplements S-012, S-014 and S-017. This submission has been sent to you today in the normal way.

We look forward to receiving the draft labeling for these supplements and have a question for you with regard to the action date (s) that the Agency is working to for these applications. Since each application was submitted at a different time and the Agency have agreed to bundle these into a single approval can you please confirm the proposed action date(s) so that I can prepare my team with regard to response times for the draft labeling.

Kind regards

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
Drug Regulatory Affairs
Novartis Oncology
Building 105/2E075
East Hanover, NJ 07936, USA
Phone: +1 862-778-2942
Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

09/22/2006 07:10 AM

To: jeremy.brace@novartis.com
cc: joseph.quintavalla@novartis.com, robert.miranda@novartis.com
Subject: RE: Gleevec pending supplements

Thanks. I have the peds. CML package ready to go, pending your response.

Re: the commitment for the multiple indications, we will need that officially submitted also. We had our first labeling meeting for these supplements (S011, 012, 013, 014, and 017) this week and the labeling is almost ready.

9/26/2006

Dotti

From: jeremy.brace@novartis.com [mailto:jeremy.brace@novartis.com]
Sent: Thursday, September 21, 2006 6:09 PM
To: Pease, Dorothy W
Cc: joseph.quintavalla@novartis.com; robert.miranda@novartis.com
Subject: RE: Gleevec pending supplements

Dear Dotti,

Many thanks for the clarification and for the update. With regard to the Pediatric labelling and postmarketing commitment —— b(4) , we will be providing you with our response in the next few days.

Kind regards

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
Drug Regulatory Affairs
Novartis Oncology
Building 105/2E075
East Hanover, NJ 07936, USA
Phone: +1 862-778-2942
Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

09/18/2006 08:30 AM

To: jeremy.brace@novartis.com
cc: joseph.quintavalla@novartis.com, robert.miranda@novartis.com
Subject: RE: Gleevec pending supplements

Thanks for your response. I'll try to answer your questions as best I can.

b(4)

b(4)

2. We look forward to receiving the draft labeling for in the coming days and that for supplements S011, S012, S013, S014 and S017 by 9-29-06.

b(4)

Please let me know your response to both ASAP. Thanks

b(4)

Dotti

From: jeremy.brace@novartis.com [mailto:jeremy.brace@novartis.com]
Sent: Thursday, September 14, 2006 12:08 PM
To: Pease, Dorothy W
Cc: joseph.quintavalla@novartis.com; robert.miranda@novartis.com
Subject: RE: Gleevec pending supplements

Dear Dotti,

b(4)

9/26/2006

We look forward to receiving the draft labeling for ——in the coming days and that for supplements S011, S012, S013, S014 and S017 by 9-29-06.

A response to the proposed postmarketing commitments regarding development of test kits will be provided to you in the next few days. b(4)

With regard to ———————————— we would appreciate some clarity as to the status of the review for this application and an understanding as to why the review is not being undertaken in parallel with the other supplements including S013 (Refractory Ph+ ALL).

Kind regards

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
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East Hanover, NJ 07936, USA
Phone: +1 862-778-2942
Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

09/07/2006 07:09 AM

To: jeremy.brace@novartis.com
cc:
Subject: RE: Gleevec pending supplements

We are having a meeting today. Originally, we thought we might be able to approve S011, S012, S013, S014,——— S017 together. But we won't be ready with the misc. supplements, so I need to separate the labeling again (which we're working on today), so that we can approve ———————— . I will probably be able to get you our draft labeling for ✓ by next week and for the others by @ 9-29-06. b(4)

I'll have to let you know about — but we are not working on labeling for it.

b(4)

Dotti

✓

9/26/2006

From: jeremy.brace@novartis.com [mailto:jeremy.brace@novartis.com]
Sent: Wednesday, September 06, 2006 4:26 PM
To: Pease, Dorothy W
Subject: Re: Gleevec pending supplements

Dear Dotti,

My apologies but when responding to the below I forgot to ask as to when we might expect draft labeling for the rare disease applications so that I can prepare the team for these discussions?

In addition can you let me know the status of the Ph+ ALL application?

Many thanks

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
Drug Regulatory Affairs
Novartis Oncology
Building 105/2E075
East Hanover, NJ 07936, USA
Phone: +1 862-778-2942
Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

Jeremy Brace 09/06/2006 04:21 PM

To: dorothy.pease@fda.hhs.gov
cc: Robert Miranda/PH/Novartis@PH, Joseph Quintavalla/PH/Novartis@PH
Subject: Re: Gleevec pending supplements Link

Dear Dotti,

Thanks for the information on the proposed PACs for our rare disease applications (MDS/MPD, SM and HES/CEL).

I will discuss these proposals within my team and provide you with a response within the next few days. In the meantime I just wanted to make sure that you were in possession of the preliminary response we provided to the Division on June 22 (email to Ann Staten, text below).

In addition I would like to point out that for MDS/MPD it is gene rearrangement of PDGFR-beta that is associated with this disease. The CHIC-2 deletion test and FIP1L1_PDGFR-alpha tests are tests for gene rearrangement of PDGFR-alpha, hence, these tests are not appropriate for MPD/MDS. A formal response with this information together with information on testing for PDGFR-beta gene rearrangements will be provided as detailed above.

Kind regards

Jeremy

9/26/2006

Dear Ann,

Further to our discussions on the availability of test kits for FIP1L1_PDGFRa for HES and for D816V Kit mutation for SM, please find below some preliminary information that we can share with you to facilitate your internal meeting on June 22.

Whilst there are no commercial test kits currently available for either FIP1L1_PDGFRa or for D816V Kit mutation there are well regarded academic institutions and reference laboratories that do provide test procedures.

FIP1L1_PDGFRa for HES

The Mayo Clinic (US) or OHSU (Oregon, US) or Hammersmith Hospital (UK) offer CHIC-2 deletion tests. The FIP1L1_PDGFRa fusion protein is formed by the deletion of CHIC-2 allowed the coding sequences for FIP1L1 and PDGFRa to be fused. Thus the absence of CHIC-2 in a patient with HES is diagnostic of the presence of the FIP1L1_PDGFRa fusion protein.

D816V Kit mutation for SM

The c-kit D816V mutation testing is available from at least 3 reference laboratories.

1) Hematologics Inc., in Seattle, WA (http://www.hematologics.com/flowcytometryservices.html#molecular3). In their b(4)
web page look under Molecular analyses - point mutation analysis.

2) Corless Laboratory in Oregon (http://www.heinrich-corless.net/services.html)

3) Quest diagnostics - Leumeta assay for c-kit mutations in mastocytosis - test code - 16104X
ttp://www.questdiagnostics.com/hcp/topics/hem_onc/leumeta.html?hem_onc)

I hope that these preliminary thoughts provide some useful information to help facilitate your internal discussion. But please bear in mind that they do not necessarily represent any formal or final position from Novartis. Discussions will continue internally in order to consider and address the Agency's views and concerns and hence any additional comments resulting from your meeting would be extremely helpful in this regard. As a consequence please take the information provided above as our preliminary thoughts that require further consideration and discussion.

Kind regards

Jeremy

Jeremy Brace, B.Sc (Hons)
Senior Associate Director
Drug Regulatory Affairs
Novartis Oncology
Building 105/2E075
East Hanover, NJ 07936, USA
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Fax: +1 973-781-5217
Email : jeremy.brace@novartis.com

9/26/2006

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

09/06/2006 11:57 AM

To: joseph.quintavalla@novartis.com, robert.miranda@novartis.com
cc:
Subject: Gleevec pending supplements

Here are the postmarketing commitments we have so far for S012, S014, and S017:

Assure availability of a validated test kit for detection of the D816V c-kit mutation. Novartis or a 3rd party should file an IDE no later than 3 months after Gleevec approval for adult Aggressive Systemic Mastocytosis and a Pre Market Application should be approved no later than 12 months after Gleevec approval for adult Aggressive Systemic Mastocytosis.
<?xml:namespace prefix = o ns = "urn:schemas-microsoft-com:office:office" />
Assure availability of a validated test kit for detection of the FIP1L1-PDGFRα fusion kinase, as determined either directly by mutational analysis or by demonstration of a CHIC2 allele deletion by FISH methodology that implies the presence of the FIP1L1-PDGFRα fusion kinase. Novartis or a 3rd party should file an IDE no later than 3 months after Gleevec approval for adult MPS/MDS and adult HES/CEL and a Pre Market Application should be approved no later than 12 months after Gleevec approval for adult MPS/MPD and adult HES/CEL.

Dotti

[Attachment "FDA VERSION LABELING 9-15-06.DOC" removed by Jeremy Brace]

9/26/2006

NOVARTIS
ONCOLOGY

jackets to MC

September 25, 2006

Robert L. Justice, M.D.
Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 21-588

GLEEVEC ® (imatinib mesylate) tablets:

Efficacy Supplements
New Indications –
MDS/MPD (S-012)
Systemic Mastocytosis (S-014)
Hypereosinophilic symdrome (S-017)

Dear Dr. Justice,

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate, formerly STI571) approved for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) and for Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to our supplemental applications for new indications for MDS/MPD (S-012, December 16, 2005), Systemic Mastocytosis (S-014, February 28, 2005) and Hypereosinophilic symdrome (S-017, March 28, 2006).

On September 6th, 2006 we received from the Agency via email (Dorothy Pease) proposed postmarketing commitments for these three supplemental applications. Please find below our response to these proposals.

S012 MDS/MPD

The imatinib sensitive target in MDS/MPD are those patients with PDGFR-beta gene rearrangements. The CHIC-2 deletion test and FIP1L1_PDGFR-alpha tests are tests for gene rearrangement of PDGFR-alpha, hence, these tests are not appropriate for MPD/MDS.

Data presented in the SNDA (S-012) show that patients with MPD/MDS associated with PDGFR-beta gene rearrangement and treated with imatinib have a reversal of the MDS/MPD disorder. Whereas imatinib administration to patients without the genetic translocation generally results in no improvement.

With regard to the development of a test kit for PDGFR-beta gene re-arrangements, it has to be considered that

b(4)

Under these circumstances Novartis is unable to commit to any post-marketing commitment to develop a validated test kit without further discussion with the Division and with the FDA Office of In Vitro Diagnostics. Hence Novartis proposes the following revised postmarketing commitment:

To meet with the Division and the FDA Office of In Vitro Diagnostics within 3 months to discuss the feasibility of a meaningful test kit for patients with MPD/MDS.

S014 Systemic Mastocytosis (SM)

Novartis agrees to the development of a validated test kit for detection of the D816v c-kit mutation. However, b(4)
the proposed timelines for the development and availability of a validated test kit. Hence, we will need to discuss this with the Division and the FDA Office of In Vitro Diagnostics in order to agree an acceptable plan and timeframe. Novartis propose the following revised postmarketing commitment:

To meet with the Division and the FDA Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the development of a validated test kit for the detection of the D816v c-kit mutation in systemic mastocytosis.

S017 HES/CEL

Novartis agrees to the development of a validated test kit for detection of the FIP1L1-PDGFR-alpha fusion protein. However, b(4)
we have some concerns over the proposed timelines for the development and availability of a validated test kit. Hence, we will need to discuss this with the Division and the FDA Office of In Vitro Diagnostics in order to agree an acceptable plan and timeframe. Novartis propose the following revised postmarketing commitment:

To meet with the Division and FDA Office of In Vitro Diagnostics within 3 months and propose a plan with timelines thereafter for the development of a validated test kit for the detection of the FIP 1L1-PDGFR-alpha fusion protein in HES/CEL.

If the Division is agreed with these proposals Novartis will contact Dr. Steve Gutman at the FDA Office of In Vitro Diagnostics to arrange a meeting with him as soon as possible as recommended by the Division.

If you have any questions or comments regarding this submission, please contact me at (862) 778-2942.

Sincerely,

JBrace

Jeremy Brace
Senior Associate Director
Drug Regulatory Affairs

/da
Submitted in triplicate

cc via e-mail: Dorothy Pease (dorothy.pease@fda.hhs.gov).

Pease, Dorothy W

From: Colangelo, Kim M
ent: Thursday, September 21, 2006 11:15 AM
o: Pease, Dorothy W; Boocker, Nancy
Subject: RE: 505(b)(2) approvals

Dotti,

Thanks for the heads up - we will proceed with clearance for all five supps at the same time.

Stay tuned,
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs, CDER, FDA
301-796-0700 (OND IO main)
301-796-0140 (direct)
301-796-9856 (facsimile)
Kim.Colangelo@fda.hhs.gov

From: Pease, Dorothy W
Sent: Thursday, September 21, 2006 10:51 AM
To: Colangelo, Kim M; Boocker, Nancy
Subject: 505(b)(2) approvals

We are preparing to approve the following 505(b)(2) efficacy supplements by Oct. 19, 2006:

NDA 21-588/S011, S-012, S-013, S-014, S-017

They are for the use of Gleevec in rare diseases and are all based, in part, on literature.

The filing reviews reflect this and are in DFS.

Thanks

Dotti

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Wednesday, September 06, 2006 11:57 AM
To: 'joseph.quintavalla@novartis.com'; 'robert.miranda@novartis.com'
Subject: Gleevec pending supplements

Here are the postmarketing commitments we have so far for S012, S014, and S017:

Assure availability of a validated test kit for detection of the D816V c-kit mutation. Novartis or a 3rd party should file an IDE no later than 3 months after Gleevec approval for adult Aggressive Systemic Mastocytosis and a Pre Market Application should be approved no later than 12 months after Gleevec approval for adult Aggressive Systemic Mastocytosis.

Assure availability of a validated test kit for detection of the FIP1L1-PDGFRα fusion kinase, as determined either directly by mutational analysis or by demonstration of a CHIC2 allele deletion by FISH methodology that implies the presence of the FIP1L1-PDGFRα fusion kinase. Novartis or a 3rd party should file an IDE no later than 3 months after Gleevec approval for adult MPS/MDS and adult HES/CEL and a Pre Market Application should be approved no later than 12 months after Gleevec approval for adult MPS/MPD and adult HES/CEL.

Dotti

9/6/2006

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, August 01, 2006 1:47 PM
To: 'joseph.quintavalla@novartis.com'
Cc: 'robert.miranda@novartis.com'; 'jeremy.brace@novartis.com'
Subject: Gleevec supplements NDA 21-588/S012 and S014

Re: your pending Gleevec supplements for MPD/MDS and mastocytosis, we have the following comment:

A Gleevec approval for MDS/MPD will require a CHIC-2 deletion test in the indication. A Gleevec approval for aggressive Systemic Mastocytosis will require the D816V Kit mutation test in the indication. This requires a regulatory status for the tests other than just being available in reference laboratories. We suggest you contact Dr. Steve Gutman, Director of the FDA Office of In Vitro Diagnostics, as soon as possible to discuss how this situation can be addressed.

Dotti for Ann Staten

From: joseph.quintavalla@novartis.com [mailto:joseph.quintavalla@novartis.com]
Sent: Tuesday, August 01, 2006 9:57 AM
To: Pease, Dorothy W
Cc: robert.miranda@novartis.com; jeremy.brace@novartis.com
Subject: RE: Gleevec information

Dear Dotti,

I am on vacation and Bob is traveling. I will try to get an answer as soon as possible, but it may take a couple of days.

Sorry for our delay

Sincerely,
Joe

"Pease, Dorothy W" <dorothy.pease@fda.hhs.gov>

07/31/2006 12:56 PM

To: joseph.quintavalla@novartis.com
cc:
Subject: RE: Gleevec information

I have the following comment from our Clin. Pharm. review on your 6-22-06 submission (s 800) to IND 55,666:

There is a discrepancy on Page 43 (table 7-2) versus Page 47 (table 7-4) regarding PK sampling

times. A six-hour time-point is mentioned for the IR formulation sampling on page 43 but is not included on page 47.

Dotti

From: joseph.quintavalla@novartis.com [mailto:joseph.quintavalla@novartis.com]
Sent: Monday, July 24, 2006 6:17 PM
To: Cross Jr, Frank H; Pease, Dorothy W
Subject: Gleevec information

Dear Captain Cross,

In my last email I had promised to send the PSUR in a separate mailing because of size. Please see attached

Best Regards,
Joe

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

/s/

Dotti Pease
8/1/2006 02:01:04 PM
CSO

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Monday, July 17, 2006 1:55 PM
To: 'robert.miranda@novartis.com'; 'joseph.quintavalla@novartis.com'
Subject: Clin. Pharm question re: Gleevec supplements

We have the following question from our clin. pharm reviewer re: Gleevec supplements, specifically all the supplements which were supported by Study B2225 (11, 12, 14, and 17).

The results in Figure 3 and Table 5 of the Summary of PK do not seem to match with regard to Day 29 Cmax for the 400 mg dose. The table reports a mean of 4207 ng/mL but the graph shows a Cmax barely reaching 4000 ng/mL. Could the company please explain the discrepancy and/or provide the data so we can do our own analysis/statistics.

If data is provided it needs to be sent in an .xpt file

Dotti Pease for Ann
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

Pease, Dorothy W

From: Fritsch, Jeff [jeff.fritsch@fda.hhs.gov]
ent: Thursday, July 13, 2006 1:18 PM
o: Jones, Michael D; Staten, Ann M
Cc: Bona, James; McCormick, John J; Pease, Dorothy W; Jones, Glen D (CDER); Friedman, Beverly J; Schwemer, Tawni B; Thakur, Emily; Vaccari, Peter
Subject: RE: NDA 21588 se1 014 Novartis Gleevec

Mike,

OOPD has determined that the proposed marketing indication fits within the scope of the designated indication and that a User Fee waiver is in order.

Regards,

Jeff Fritsch, RPh
CDR, U.S. Public Health Service
Regulatory Review Officer
Office of Orphan Products Development

From: Jones, Michael D
Sent: Monday, July 10, 2006 12:25 PM
To: Staten, Ann M; Fritsch, Jeff
Cc: Bona, James; McCormick, John J; Pease, Dorothy W; Jones, Michael D; Jones, Glen D (CDER); Friedman, Beverly J; Schwemer, Tawni B; Thakur, Emily
Subject: NDA 21588 se1 014 Novartis Gleevec

Looks like we received SE1 014 to Novartis' Gleevec. It also looks like they claim they do not have to pay a fee based on the orphan exemption.

I checked the Orphan web site and it shows:

	Generic Name: Designation:	
	Imatinib mesylate	Treatment of systemic mastocytosis without the D816V c-kit mutation
	Trade Name (if present):	***Sponsor Contact Information***
	Gleevec	Novartis Pharmaceuticals Corporation
Date Designated	9/9/2005	One Health Plaza
Date Approved	East Hanover NJ	07936-1080

I also checked the proposed Indications and Usage section and it states a (proposed in red):

INDICATIONS AND USAGE

Gleevec® (imatinib mesylate) is indicated .....

---

b(4)

It looks like they have proposed an indication that is outside the scope of their designation when they state that Gleevec is indicated when the cKit mutational status is unknown. Can you folks confirm that what is proposed is outside the orphan designation?

Thanks

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-588 Supplement # 014, 017 Efficacy Supplement Type SE- 1

Trade Name: Gleevec
Established Name: (imatinib mesylate)
Strengths: Tablets

Applicant: Novartis
Agent for Applicant: Joseph Quintavalla

Date of Application: February 28, 2006 and March 28, 2006
Date of Receipt: March 1, 2006 and March 29, 2006
Date clock started after UN:
Date of Filing Meeting: April 13, 2006
Filing Date: April 30, 2006 and May 28, 2006
Action Goal Date (optional): User Fee Goal Date: January 1, 2007 and January 29, 2007

Indications requested:
Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ✓ x2

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ✓ NDA is a (b)(2) application

Therapeutic Classification: S ✓ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) Orphan drug designation

Form 3397 (User Fee Cover Sheet) submitted: YES ✓ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ✓
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ✓ NO ☐
  If yes, explain: The sponsor already has existing exclusivity under NDA 21-588

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ✓

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ✓
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ✓ NO ☐

- Was form 356h included with an authorized signature? YES ✓ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ✓ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ✓ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? all

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ✓ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ✓ YES ☐ NO
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ✓ NO ☐

- Exclusivity requested? YES, ✓ Years 5 ☐
  _____ NO

  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ✓ NO ☐

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES ✓ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ✓ ☐ NO ☐

  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 55,666

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ■
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 8-12-04 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ✓ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ✓ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ✓ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ✓ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ✓ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ✓ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 13, 2006

BACKGROUND:

ATTENDEES: Robert Justice, Acting Director; Ann Farrell, MD, Acting Deputy Director; John Johnson, MD, Medical Team Leader; Marty Cohen, MD, Medical Reviewer (via phone); Raji Sridhara, PhD, Stat. Team Leader; Shenghui Tang, PhD, Stat. Reviewer, Brian Booth, PhD, Acting Clin Pharm Team Leader; Julie Bullock, PhD, Clin Pharm Reviewer;

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Martin Cohen, MD
Secondary Medical:	John Johnson, MD
Statistical:	Shenghui Tang, PhD
Pharmacology:	n/a
Statistical Pharmacology:	n/a
Chemistry:	Chengyi Liang, PhD
Environmental Assessment (if needed):	yes
Biopharmaceutical:	n/a
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
Clinical Pharmacology:	Julie Bullock
DSI:	N/A
Regulatory Project Management:	Ann Staten, RD
Other Consults:	Joe Grillo, DDMAC

Per reviewers, are all parts in English or English translation? YES ✓ NO ☐
If no, explain:

CLINICAL FILE ✓ REFUSE TO FILE ☐

- Clinical site inspection needed? YES NO ✓ ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ✓
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A x ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ✓ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ✓ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ✓ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ✓

PHARMACOLOGY N/A ✓ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ✓ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: no ODA, No DSI

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

✓ ☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

✓ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ✓ Convey document filing /no filing issues to applicant by Day 74. (done)

Ann Staten, RD
Regulatory Project Manager, HFD-150

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ✓ ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ✓ ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ✓ ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ✓ ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ✓ ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). new indications

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ✓ ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ✓ ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

✓ ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ✓ ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ✓ ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ✓ ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ✓ ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# 55,666 NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ✓ ☐ NO ☐

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/s/

Ann Staten
6/7/2006 12:16:41 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*)	FROM:
DMAC, HFD-42 – Joe Grillo	Ann Staten

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-10-06		21-588/S-014 ,16,17	New sNDAs	2-28-06;-27-06;3-28-06

DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gleevec (imatinib mesylate)	Labeling meeting 6-15-06		Prior to labeling meeting

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER (fax)
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURINGCHANGE/ADDITION	☐ CONTROL SUPPLEMENT	■ OTHER *(SPECIFY BELOW)*
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: We have 3 new sNDAs in the EDR. Marty Cohen is the medical reviewer. The submissions in the EDR are S-014, —— and 017.

)14 and 017 are combined with 011, 012, 013, —— now for – indications to be discussed at the 6-15-06 labeling meeting.) ——————————————— b(4)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Ann Staten	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-588/S-014, S-017

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

Attention: Joseph Quintavalla
Senior Regulatory Manager
Drug Regulatory Affairs

Dear Mr. Quintavalla:

Please refer to your February 28 (S-014) and March 28 (S-017), 2006 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate).

We also refer to your submission dated April 7, 2006.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, the application S-014 was filed on April 30, 2006 and the application S-017 will be filed under section 505(b) of the Act on May 28, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the applications and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Ann M. Staten, R.D.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ann Staten
5/2/2006 01:44:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S-014, S-017

PRIOR APPROVAL SUPPLEMENT

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

Attention: Joseph Quintavalla
Senior Regulatory Manager
Drug Regulatory Affairs

Dear Mr. Quintavalla:

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

Name of Drug Product: Gleevec (imatinib mesylate)

NDA Number: 21-588

Supplement numbers: S-014 and S-017

Review Priority Classification: Standard (S)

Date of supplements: February 28, 2006 (S-014) and March 28, 2006 (S-017)

Date of receipts: March 1, 2006 (S-014) and March 29, 2006 (S-017)

These supplemental applications propose the following new indications:

1. For the treatment of patients with Systemic Mastocytosis (SM) without the D816V c-kit mutation.
2. For the treatment of patients with hypereosinophilic syndrome (HES).

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on April 30, 2006 (S-014) and May 28, 2006 (S-017) in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal dates will be January 1, 2007 (S-014) and January 29, 2007 (S-017).

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your requests for a waiver of pediatric studies for the applications. Once the applications have been filed we will notify you whether we have waived the pediatric study requirement for the applications.

Please cite the application number listed above at the top of the first page of all submissions to the applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Ann M. Staten, R.D.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ann Staten
4/14/2006 01:00:22 PM

NOVARTIS
ONCOLOGY

March 28, 2006

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsvillle, MD 20705-1266

No. 21-588

GLEEVEC ® (imatinib mesylate) tablets

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

NEW INDICATION – HYPEREOSINOPHILIC SYNDROME

Dear Dr. Justice;

Reference is made to our NDA 21-335 for Gleevec® (imatinib mesylate, formerly STI571) approved for the treatment of patients with Philadelphia chromosome (Ph+) chronic myeloid leukemia (CML), and for Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

At this time Novartis Pharmaceuticals Corporation submits a supplemental New Drug Application (sNDA) for the use of Gleevec in a new indication for the treatment of patients with hypereosinophilic syndrome (HES). This sNDA consists of essential data from a Novartis Phase II trial (CSTI571B2225) and additional data from publications in peer reviewed journals as agreed upon in a Type B meeting on August 12, 2004. Four rare diseases (including HES) were addressed at that meeting, and were investigated in B2225. At the request of the FDA, (Ann Staten to Robert Miranda, July 21, 2005) each of the four rare disease indications are being submitted separately.

Request for Priority Review

Gleevec is intended for the treatment of patients with hypereosinophilic syndrome. This is a medical condition that is very rare (Orphan designation No. 05-2090) and for which there is a clear unmet medical need. The clinical data demonstrate that Gleevec provides very high response rate in HES patients. Gleevec is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis. Given this profile and the innovative, rational design and well understood mechanism of action, Novartis believes that this application qualifies for priority review according to CDER's MAPP 6020.3, in that

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-588 Supplement # 013 and — Efficacy Supplement Type SE- 1

b(4)

Trade Name: Gleevec
Established Name: (imatinib mesylate)
Strengths: Tablets

Applicant: Novartis
Agent for Applicant: Joseph Quintavalla

Date of Application: December 20, 2005 x2
Date of Receipt: December 21, 2005 x2
Date clock started after UN:
Date of Filing Meeting: February 8, 2006
Filing Date: February 18, 2006
Action Goal Date (optional): User Fee Goal Date: 10-21-06 x2

Indication(s) requested:
S-013:Adult patients with Ph+ALL as monotherapy for relapsed and/or refractory patients.

b(4)

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ✓

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ✓ NDA is a (b)(2) application

Therapeutic Classification: S ✓ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) Orphan drug designation

Form 3397 (User Fee Cover Sheet) submitted: YES ✓ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ✓
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity*

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ✓ NO ☐
  If yes, explain: The sponsor already has existing exclusivity under NDA 21-588

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ✓

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ✓
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ✓ NO ☐

- Was form 356h included with an authorized signature? YES ✓ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ✓ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ✓ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance?
  N/A ✓ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ✓
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ✓ NO ☐

- Exclusivity requested? YES, ✓ Years 5 ☐
  _____ NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES ✓ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES ✓ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ✓ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 55,666

- End-of-Phase 2 Meeting(s)? Date(s) January 10, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 10, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ✓ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ✓ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ✓ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ✓ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ✓ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ✓ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 8, 2006

BACKGROUND: Gleevec (imatinib mesylate) was approved in May 2001 for . The sponsor has submitted the two sNDAs for review following the EOP1 meeting.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Robert Justice, Acting Director; Ramzi Dagher, MD, Acting Deputy Director; John Johnson, MD, Medical Team Leader; Marty Cohen, MD, Medical Reviewer; Hun Ke, PhD, Stat. Reviewer; Sophia Abraham, PhD, Clin Pharm Reviewer;

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Martin Cohen, MD
Secondary Medical:	John Johnson, MD
Statistical:	Hun Ke, PhD
Pharmacology:	n/a
Statistical Pharmacology:	n/a
Chemistry:	
Environmental Assessment (if needed):	yes; Chengyi Liaing, PhD
Biopharmaceutical:	n/a
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	Lloyd Johnson, PharmD
Regulatory Project Management:	Ann Staten, RD
Other Consults:	Joe Grillo, DDMAC

Per reviewers, are all parts in English or English translation? YES ✓ NO ☐
If no, explain:

CLINICAL FILE ✓ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ✓ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ✓
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ✓ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ✓ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE N/A✓ ☐ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ✓

PHARMACOLOGY N/A ✓ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ✓ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

✓ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ✓ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3✓ Convey document filing issues/no filing issues to applicant by Day 74. done

Ann Staten, RD
Regulatory Project Manager, HFD-150

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ✓

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ✓

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ✓

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ✓

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ✓

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ✓

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

✓ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ✓ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ✓ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ✓ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ✓ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# 55,666 NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ✓ NO ☐

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
3/15/2006 08:06:46 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	February 7, 2006
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(862) 778-0233	(973) 781-5217
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
One Health Plaza East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) **21-588**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY	
imatinib mesylate	**Gleevec**	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)		CODE NAME (*If any*) **STI571**
DOSAGE FORM: **Tablet**	STRENGTHS: **100 & 400 mg**	ROUTE OF ADMINISTRATION: **Oral**

(PROPOSED) INDICATION(S) FOR USE:
CML and GIST

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

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

TYPE OF SUBMISSION (*check one*) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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

REASON FOR SUBMISSION
Minor Amendment To Pending A Application

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

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

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

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

IND 55,666
NDA 21-335
NDA 21-588

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

CERTIFICATION

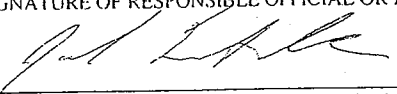
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660. and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
☒ 	Joseph Quintavalla, Phd Senior Manager Drug Regulatory Affairs	2/7/06

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(862) 778-0233

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

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

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr.,Room 3046
Rockville, MD 20852

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

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-588 Supplement # 011 and 012 Efficacy Supplement Type SE- 1

Trade Name: Gleevec
Established Name: (imatinib mesylate)
Strengths: Tablets

Applicant: Novartis
Agent for Applicant: Joseph Quintavalla

Date of Application: December 16, 2005 x2
Date of Receipt: December 19, 2005 x2
Date clock started after UN:
Date of Filing Meeting: February 8, 2006
Filing Date: February 17, 2006 x2
Action Goal Date (optional): User Fee Goal Date: September 19, 2006

Indications requested: adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma (DFSP) and adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ✓x2

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ✓ NDA is a (b)(2) application

Therapeutic Classification: S ✓x2 P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) Orphan drug designation

Form 3397 (User Fee Cover Sheet) submitted: YES ✓ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ✓
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ✓ NO ☐
  If yes, explain: The sponsor already has existing exclusivity under NDA 21-588

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ✓

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ✓
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ✓ NO ☐

- Was form 356h included with an authorized signature? YES ✓ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ✓ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ✓ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? all

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ✓ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ✓ YES ☐ NO
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ✓ NO ☐

- Exclusivity requested? YES, ✓ Years 5 ☐
  NO

  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ✓ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ✓ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☐ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 55,666

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ■
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 8-12-04 x2 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ✓ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ✓ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ✓ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ✓ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ✓ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ✓ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 8, 2006

BACKGROUND: Gleevec (imatinib mesylate) was approved in May 2001 for patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma (DFSP)and adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

ATTENDEES: Robert Justice, Acting Director; Ramzi Dagher, MD, Acting Deputy Director; John Johnson, MD, Medical Team Leader; Marty Cohen, MD, Medical Reviewer; Hun Ke, PhD, Stat. Reviewer; Sophia Abraham, PhD, Clin Pharm Reviewer;

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Martin Cohen, MD
Secondary Medical:	John Johnson, MD
Statistical:	Hun Ke, PhD
Pharmacology:	n/a
Statistical Pharmacology:	n/a
Chemistry:	Chengyi Liang, PhD
Environmental Assessment (if needed):	yes
Biopharmaceutical:	n/a
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
Clinical Pharmacology:	Sophia Abraham
DSI:	Lloyd Johnson, PharmD
Regulatory Project Management:	Ann Staten, RD
Other Consults:	Joe Grillo, DDMAC

Per reviewers, are all parts in English or English translation? YES ✓ NO ☐
If no, explain:

CLINICAL FILE ✓ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ✓ For DFSP only ☐ NO
- Advisory Committee Meeting needed? YES, date if known _____ NO ✓
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ✓ FILE ☐ REFUSE TO FILE ☐

STATISTICS	N/A ☐	FILE ✓			REFUSE TO FILE ☐	
BIOPHARMACEUTICS FILE		✓	For B2225 study		REFUSE TO FILE ☐	
• Biopharm. inspection needed?				YES ☐	NO ✓	
PHARMACOLOGY	N/A ✓	FILE ☐		REFUSE TO FILE ☐		
• GLP inspection needed?				YES ☐	NO ☐	
CHEMISTRY		FILE ✓			REFUSE TO FILE ☐	
• Establishment(s) ready for inspection?				YES ☐	NO ☐	
• Microbiology				YES ☐	NO ☐	

ELECTRONIC SUBMISSION:
Any comments: Clinical Pharmacology request to be sent by email.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

✓ ☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

✓ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. ✓ Convey document filing issues/no filing issues to applicant by Day 74 (done).

Ann Staten, RD
Regulatory Project Manager, HFD-150

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ✓ ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ✓ ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ✓ ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ✓ ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ✓ ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). new indications

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ✓ ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ✓ ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

✓ ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ✓ ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ✓ ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ✓ ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ✓ ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# 55,666 NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ✓ ☐ NO ☐

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
3/14/2006 03:04:16 PM
CSO

NOVARTIS
ONCOLOGY

February 28, 2006

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsvillle, MD 20705-1266

No. 21-588

GLEEVEC ® (imatinib mesylate) tablets

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

NEW INDICATION – SYSTEMIC MASTOCYTOSIS (SM)

Dear Dr. Justice;

Reference is made to our NDA 21-335 for Gleevec® (imatinib mesylate, formerly STI571) approved for the treatment of patients with Philadelphia chromosome (Ph+) chronic myeloid leukemia (CML), and for Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

At this time Novartis Pharmaceuticals Corporation submits a supplemental New Drug Application (sNDA) for the use of Gleevec in a new indication for the treatment of patients with Systemic Mastocytosis (SM) without the D816V c-kit mutation. This sNDA consists of essential data from a Novartis Phase II trial (CSTI571B2225) and additional data from publications in peer reviewed journals as agreed upon in a Type B meeting on August 12, 2004. Four rare diseases (including SM) were addressed at that meeting, and were investigated in B2225. At the request of the FDA, (Ann Staten to Robert Miranda, July 21, 2005) each of the four rare disease indications are being submitted separately.

Request for Priority Review

Gleevec is intended for the treatment of patients with SM without the D816V c-kit mutation. This is a medical condition that is very rare (Orphan designation No. 05-2092) and for which there is a clear unmet medical need. The clinical data demonstrate that Gleevec provides very high response rate in SM patients without the D816V c-kit mutation. Gleevec is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis. Given this profile and the innovative, rational design and well understood mechanism of action, Novartis believes that this application qualifies for priority

review according to CDER's MAPP 6020.3, in that Gleevec offers a significant improvement in the treatment of SM, a serious and life-threatening condition, compared to available historical therapies.

We believe that this application will entitle Gleevec to a 5 year period of exclusivity base on the new data from the Novartis study (B2225) that are essential to approval of this supplement and support for the indication.

The Gleevec formulation is the same as previously approved for CML and GIST, and therefore, there is no preclinical or technical information in this sNDA. There are no changes to the chemistry, non-clinical pharmacology, toxicology, human pharmacokinetics and bioavailability sections. The CMC section is limited to an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of section 3 is being provided to our district office.

This submission is being provided in accordance with the guidance for industry titled, Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). The relevant technical details of the electronic portions of this submission are as follows:

• Submission size:	approximately 204 MB
• Electronic media:	1 compact disc
• Virus scan:	Network Associates Incorporated VirusScan© version 4.5.1 (formerly known as the McAfee VirusScan). The submission is virus free.

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

If you have any questions or comments, please contact me at 862-778-0233.

Sincerely,

Joseph Quintavalla, Ph.D.
Senior Regulatory Manager

Attachments: Electronic Submission; one CD plus paper cover letter

Desk Copy via fax (cover letter only): Ann Staten (HFD-150 at 301-796-9845)

Staten, Ann M
From: Staten, Ann M
Sent: Monday, February 13, 2006 1:20 PM
To: 'robert.miranda@novartis.com'
Cc: 'joseph.quintavalla@novartis.com'
Subject: Gleevec information request PK reviewer

Hi Bob,

The clinical pharmacology reviewer requests the following:

1. Please submit the raw PK data for Study B2225

2. Please correlate the dose and pharmacokinetic (PK) parameters, as well as the changes in imaging/molecules with the clinical efficacy/safety endpoints in Study B2225, as requested at the EOP1 meeting on 12-Aug-2004.

Thanks,
Ann

****

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867
ann.staten@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S-011, S-012, S-013

PRIOR APPROVAL SUPPLEMENT

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

Attention: Joseph Quintavalla
Senior TA Manager
Drug Regulatory Affairs

Dear Mr. Quintavalla:

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

Name of Drug Product: Gleevec (imatinib mesylate)

NDA Number: 21-588

Supplement numbers: S-011 (DFSP), S-012 (MDS/MDP), S-013 (Ph+ ALL)

Review Priority Classification: Standard (S)

Date of supplements: December 16 and 20, 2005

Date of receipts: December 19 and 21, 2005

These supplemental applications propose the following new indications:

1. For the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
2. For the treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
3. _____ b(4) _____ as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on February 17 (S-011, S-012)

and 18 (S-013), 2006 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal dates will be September 19 (S-011 and S-012) and September 21 (S-013), 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your requests for a waiver of pediatric studies for the applications. Once the applications have been filed we will notify you whether we have waived the pediatric study requirement for the applications.

Please cite the application number listed above at the top of the first page of all submissions to the applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Ann M. Staten, R.D.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Ann Staten
2/9/2006 09:04:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-588/S-011, S-012, S-013

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

Attention: Joseph Quintavalla
Senior TA Manager
Drug Regulatory Affairs

Dear Mr. Quintavalla:

Please refer to your December 16 and 20, 2005 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate).

We also refer to your submissions dated January 24, February 6, 7 and 8, 2006.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on February 17 (S-011 and S-012) and 18, 2006 (S-013) in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the applications and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Ann M. Staten, R.D.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Ann Staten
2/9/2006 09:13:09 AM

NOVARTIS
ONCOLOGY

February 7, 2006

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 21-588 S-011
NDA No. 21-588 S-012
NDA No. 21-588 S-013

GLEEVEC ® (imatinib mesylate)

Minor Amendment to a Pending Application

Dear Dr. Justice, MD

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate) approved for the treatment of patients with Philadelphia chromosome positive, chronic myeloma leukemia, and with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. Reference is also made to the NDA supplementsS-011, S012 and S-013 which provide for the new indications of Dermatofibrosarcoma Protuberans (DFSP), Myelodysplastic Syndrome / Myeloproliferative Diseases, and for Acute Lymphoblastic Leukemia (New Indications), respectively. These supplements rely on data from both Novartis sponsored studies and published articles.

In response to a phone call from Ann Staten on February 6, 2006, we are submitting this minor amendment to each of the pending sNDAs in order to provide a 505b(2) certification as it pertains to the use of published articles using Gleevec in their studies. Pursuant with CFR 314.50 i(1)ii, Novartis is the sole owner of Gleevec patents, and there are no patents in our application claiming the use of Gleevec for the treatment of any of the New Indications that would be infringed upon.

Certification:
In the opinion and to the best knowledge of Novartis Pharmaceuticals Corporation, there are no patents, other that those belonging to Novartis, that claim the drug on which investigations that are relied upon in this application were conducted or that claim a use of such drug for the treatment of any of the New Indications.

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

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

If you have any questions or comments regarding this submission, please contact me at (862) 778-0233.

Sincerely,

Joseph Quintavalla, Ph.D.
Senior Manager
Drug Regulatory Affairs

Submitted in duplicate

Desk Copy via fax (cover letter only): Ann Staten (301-796-9845)

DRAFT

February x, 2006

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsvillle, MD 20705-1266

No. 21-588/S-013

GLEEVEC ® (imatinib mesylate) tablets

MINOR AMENDMENT TO A PENDING APPLICATION

(NEW INDICATION: Ph+ ALL)

Dear Dr. Justice:

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate) and our efficacy supplement S-013 dated December 20, 2005. This supplement provided a new indication

b(4)

_____ as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL.

At this time we would like to provide data in respond to two reviewer requests received on January 18, 2006 from Ann Staten as follows:

FDA Comment:

"Please present separate data for the 48 patients with Ph+ ALL from the 8 patients with CML-LBC in study 0109. If datasets had previously been submitted with an earlier NDA, please submit them again."

Novartis Response:

Please find below a summary of analysis conducted and available in various Clinical Study Reports (CSR) previously submitted:

- In the original NDA 21-335, dated February 27, 2001, the CSR for study 109 (using data cut-off 09-Oct-2000; dated 07-Feb-2001), provided all post-text tables (PTTs) summarizing the overall 293 patients in study 0109 and then split these into accelerated phase (AP) CML (n=235), AML (n=2) as well as LBC (n=8) and ALL (n=48). Post-text listings (PTLs) were provided by disease (and patient).

- Data for LBC (n=8) and ALL (n=48) have been published by Ottmann (Ottmann OG, Druker BJ, Sawyers CL, et al. Blood 2002; 100: 1965-1971) based on data cut-off 31-Jan-2001 (with some re-assignment of responses by the first author).
- The final CSR (using data cut-off 31-July-2002; dated 16-Dec-2002) was then split by disease group as well (AP-CML, AML, LBC, ALL). This CSR and all the post-text deliverables (Post-text supplement 3) were submitted to NDA 21-335 on December 20, 2002 as part of the fulfillment of post-market commitment #2, which lead to full approval of our advanced Ph+ CML indications. This CSR is provided again as an attachment to this submission, but is limited to the core report and post-text supplement 3.
- It should be noted, that after the 31-July-2002 cut-off, only dosage administration, SAEs and survival follow-up were recorded in the database for this study (but no concomitant medications, laboratory values and AEs). Therefore the 2002 CSR which is now being re-submitted could be used to review safety and efficacy results by disease subtype (LBC vs ALL). Usually the same numbering of post-text tables had been used; therefore the sources in the LBC & ALL report submitted in December 2005 usually correspond to the post-text table numbers in the re-submitted 2002 CSR.
- The SAS datasets included in the CRTs of the 2005 submission for LBC & ALL include a variable named TYPECALC ('Calculated type of leukemia') in all the datasets which is =4 (LBC) or =5 (ALL) and thus could be used for subset analyses if these would be done electronically.
- The 2005 CSR for study 0109 (on all LBC and ALL patients) includes a post-text listing (PTL 7.1-1) which lists the patient identifiers together with the disease subtype (LBC or ALL). This could be used to identify individual patients in that CSR. However, in the 2002 CSR, all post-text listings include the disease group and thus would allow the review of efficacy and safety data by disease.
- In the 2002 CSR – and thus listed by disease - the main efficacy data (to verify response) for individual patients is included in PTL 9.2-1 (hematologic response) and PTL 9.1-2 (cytogenetic response). The derived responses are listed in PTL 9.2-1 and 9.2-2 per patient.
- The main safety data is listed by disease and patient in PTLs in Section 3.5 of PTS3 (relating to text section 10).

FDA Comment:

"For the phase 1 study 03 001, do you have separate data for patients in lymphoid blast crisis and for patients with ALL? The New England Journal report combines all patients with a lymphoid phenotype."

Novartis Response:

Please find below a summary of analysis conducted and available in various CSRs previously submitted:

- In the original NDA 21-335, dated February 27, 2001, the CSR for study 03 001 (using data cut-off 06-May-2000; dated 26-Jan-2001) provided all post-text tables splitting the 149 patients in study 03 001 into 84 patients with adult chronic leukemia, 59 patients with adult acute phase leukemia and 6 pediatric patients. This CSR is provided again

as an attachment to this submission, but is limited to the core report and post-text supplement 3..

- The 59 adult patients with acute phase leukemia included patients with AML (n=1), MBC (n=38) as well as LBC (n=10) and ALL (n=10). PTL 7.1-1 identifies the patients by subtype of acute leukemia. This could be used to identify patients with LBC and ALL.
- The only information provided by this subtype is the efficacy data in PTL 9.2-1 which is then summarized in PTT 9.2-1 and in-text Table 9-6.
- The New England Journal report (Druker BJ, Talpaz M, Resta DJ, et al. N Eng J Med; 2001; 344: 1031-1037) is based on the 58 patients with either MBC (n=38), LBC (n=10) and ALL (n=10) using the data described in the CSR. Table 5 in that paper describes the responses in the 20 patients with LBC and ALL. The split by disease could then be obtained in the CSR in PTT 9.2-1 (and PTL 9.2-1) as described above.
- The generation of new safety tables by disease subtype (instead of the currently 59 patients with acute leukemia being combined) would take at least several days. It would therefore be of great help, if the FDA could specify which of the PTTs included in the re-submitted 03 001 CSR would be required for LBC vs ALL.

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005). The relevant technical details of the electronic portions of this submission are as follows:

• **Submission size:**	approximately xxx MB
• **Electronic media:**	four compact discs
• **Virus scan:**	Network Associates Incorporated VirusScan© version 7.1.0 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or comments regarding this submission, please contact me at 862-778-2282.

Sincerely,

Robert Miranda
Director
Drug Regulatory Affairs

Attachments:

1) Clinical Study Report for 0109, dated 16-Dec-2002 (core report and post-text supplement 3)

2) Clinical Study Report for 03 001, dated 26-Jan-2001(core report and post-text supplement 3)

cc (cover letter only): Ann Staten via e-mail (statena@cder.fda.gov)

Staten, Ann M

From: robert.miranda@novartis.com
Sent: Monday, January 30, 2006 2:03 PM
To: Staten, Ann M
Subject: Re: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Ann,

As promised attached is our further response to this reviewer question of January 13, 2006. I hope our response is acceptable. Please let me know if you have any questions or comments. A formal copy of this response will be sent to the NDA.

Thanks,
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
Assistant: [redacted] b(6)
****

----- Forwarded by Robert Miranda/PH/Novartis on 01/30/2006 01:56 PM -----

Robert Miranda
01/24/2006 12:10 PM

To: statena@cder.fda.gov
cc:
Subject: Re: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Hi Ann,

Just to give you an update on our pending response. This is taking a little more time than expected and I should have a response for you by Monday. I hope this is OK but I wanted to make sure the response was complete and provided roadmaps to the data for the reviewer.

Thanks
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
Assistant: [redacted] b(6)

---- Forwarded by Robert Miranda/PH/Novartis on 01/24/2006 12:05 PM ----

Robert Miranda

01/17/2006 12:29 PM

To: statena@cder.fda.gov
cc: Joseph Quintavalla/PH/Novartis@PH
Subject: Re: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Ann,

Regarding the remaining comment received on 1/13/06 (see below), we are preparing a patient profile for each of the 7 MDS/MPD patients in study 2225 in order to address the reviewer's comment. These profiles will define the clinical response (hematologic and cytogenetic) with specific references to data listings (by # and page) and to supportive publications as appropriate. This should clearly provide a roadmap linking the data in our submission to the response in our Appendix 7 consistent with the proposed labeling. We plan to send this to you by Monday.

FDA Comment: We still cannot confirm responses of MDS/MPD patients. The patient data in the BMA database does not include all of the dates listed in Appendix 7.1, pages 615-616 or 1168, or pages 90-91.

Thank you for your patience.

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
Assistant: [redacted] b(6)

---- Forwarded by Robert Miranda/PH/Novartis on 01/17/2006 12:18 PM -----

Robert Miranda

01/13/2006 03:51 PM

To: "Staten, Ann M" <STATENA@cder.fda.gov>
cc: Joseph Quintavalla/PH/Novartis@PH
Subject: Re: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)Link

Dear Ann,

Sorry for any misunderstandings. I have spoken with the clinical and biostat persons (they are in Switzerland) and I can clarify one of your two comments as follows:

FDA Comment: The hematology results from Appendix 7.1 do not specifically identify MDS/MPD patients.

Novartis Clarification:

Appendix 1.7 (Listing 1-21: Laboratory Test Results) is organized first by "Laboratory Group" (i.e. biochemistry or hematology) then by indication. Therefore the MDS/MPD patients are found under "hematology malignancy", then "Myeloproliferative disorder". This begins on page 5224 of Appendix 7. (Sorry, but I provided you with the wrong page reference in my original response.)

I am still waiting for a response from my team on the other comment and I should have a clarification on Monday.

Thanks

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
Assistant: [redacted]
****

b(6)

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

01/13/2006 10:38 AM

To: Robert Miranda/PH/Novartis@PH
cc: Joseph Quintavalla/PH/Novartis@PH

Subject: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Bob,

We still cannot confirm responses of MDS/MPD patients. The patient data in the BMA database does not include all of the dates listed in Appendix 7.1, pages 615-616 or 1168, or pages 90-91. The hematology results from Appendix 7.1 do not specifically identify MDS/MPD patients.

Please clarify.

Thanks,
Ann

-----Original Message-----
From: robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]
Sent: Thursday, January 12, 2006 12:53 PM
To: Staten, Ann M
Cc: joseph.quintavalla@novartis.com
Subject: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Ann,

The following response is made to your information request of 1/5/06:

FDA Reviewer's Question

"We are having a hard time confirming responses of the 7 MDS/MPD patients in study B2225 using the submitted datasets. Please provide serial hematology and bone marrow data for each of the 7 patients."

Novartis Reply

The derived datasets which contain all the relevant tumor evaluation information are the following

"A_TUM.sas": Assessment of Tumor Response
"A_TUMD.sas": Tumor description
"A_TUMA.sas": Tumor Assessment
"A_TUMC.sas": Tumor Assessment Comments

These datasets are included in the Case Report Tabulations, as well as the description of variables (Item 11 in this sNDA).

Please consider the following patient data listings and post-text tables (Appendix 7 and Supplement 3, respectively, of the Clinical Study Report for 2225 in Item 8 of this sNDA) carried out using the above data:

- **Appendix 7.1 Listing 1-14: Response Assessment, by Visit, Indication and Malignancy Type (page 586 of Appendix 7):**

  This lists, by MPD/MDS patients, all the assessments of tumor response per visit along with the date of assessment and the actual study day. Post-Text Table 9.1-1 is derived from the information contained in this listing.

- **Post-Text Table 9.1-1: Assessment of Tumor Response, by Visit, Indication and Malignancy Type (page 1060 of Supplement 3):**

This tabulates the assessment of tumor response by visit and provides as well the tabulation of the best overall response. Note that the assessment at each evaluation is based on investigator's evaluation of the objective tumor status and not on recalculated response.

The requested information on hematology parameters is contained in the following listing

- **Appendix 7.1 Listing 1.21: Laboratory Test Results, by Indication and Malignancy Type (page 1455 of Appendix 7):**

This lists, by MDS/MPD patients, the Lab Biochemistry test results by parameter. Also contained in this listing is the more important hematology test results for MDS/MPD patients (page 3807).

- **Post-Text Table 10.3-3: Hematology Results by Visit and Malignancy Type (page 1441 of Supplement 3)**

This tabulates descriptive summary indices of hematology parameters by visit and by malignancy type.

I hope this is helpful. Please let me know if you have any questions or comments. A formal copy of this response will be sent to the NDA.

Thanks,
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
Assistant: [redacted] b(6)

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

01/05/2006 12:17 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: information request - NDA 21-588/S-

Dear Bob,

- We have the following request from the medical reviewer for the MDS/MPD supplement (S-012).

- We are having a hard time confirming responses of the 7 MDS/MPD patients in study B2225 using the submitted datasets.

- Please provide serial hematology and bone marrow data for each of the 7 patients.

- Sincerely,

- Ann

- P.S. DFSP was assigned S-011 and ALL was assigned S-013

Staten, Ann M

From: robert.miranda@novartis.com
Sent: Monday, January 30, 2006 6:19 PM
To: Staten, Ann M
Subject: Re: Information request - NDA 21-588 S013

Hi Ann,

Just an update. I was told today that re-submission of these two reports would span many volumes so we are going to submit it electronically. However, since one of the reports was several years old we will have to scan documents to accomplish this. The bottom line is that it will take another week to get the reports to you. In the meantime I would like to share with you the coverletter that will accompany these two reports, which contains the answers to the reviewer's questions. I hope this helps facilitate the review.

Thanks
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
Assistant: [redacted] b(6)
****

Hi Ann,

Since these two requests require re-submission of the study reports for study 03-001 and 109, I need until Monday to get these out to you. I hope this is OK.

Bob.....

---- Forwarded by Robert Miranda/PH/Novartis on 01/24/2006 01:30 PM ----

Robert Miranda

01/18/2006 04:41 PM

To: "Staten, Ann M" <STATENA@cder.fda.gov>
cc: Joseph Quintavalla/PH/Novartis@PH
Subject: Re: Information request - NDA 21-588 S013Link

Hi Ann,

I have forward this request and the previous one to our team for a response.

Thanks
Bob

Robert A. Miranda, R.A.C.
Director
Drug Regulatory Affairs
Oncology Business Unit
Building 1057 Room 2W200
East Hanover, New Jersey 07936
Phone: 862-778-2282
Fax: 973-781-5217
E-mail: Bob Miranda
Assistant: [redacted] b(6)

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

01/18/2006 04:02 PM

To: Robert Miranda/PH/Novartis@PH
cc: Joseph Quintavalla/PH/Novartis@PH
Subject: Information request - NDA 21-588 S013

Dear Bob,

We have an additional information request:

Please present separate data for the 48 patients with Ph+ALL from the 8 patients with CML-LBC in study 0109. If datasets had previously been submitted with an earlier NDA, please submit them again.

Thanks,

Ann

Patient —— 901/177

Age/Sex/Race=57/F/CA, Start=10JUN2003, End=06JUL2004 b(6)

Patient —— /901/177 presented at screening with abnormal CBC, including hemoglobin and platelet below lower limit of normal (10.6 g/L and 125 10E9/L, respectively) and elevated WBC (99.6 10E9/L). The CBC reached normal levels approximately four months after screening, which were sustained through the end of the study. The investigator assessed the patient as achieving a partial hematological response approximately two months after enrollment. A follow-up bone marrow evaluation was not performed. Novartis agrees with the investigator's assessment. b(6)

Investigator's assessments of hematology, bone marrow, and tumor response – Study B2225, Patient —— /901/177: b(6)

Visit and Date	Hemoglobin[a] (g/L)	WBC[b] (10E9/L)	Platelets[c] (10E9/L)	Bone marrow[d]	Investigator assessment of tumor response[e]
V1 30MAY2003	10.6 L	99.6 H	125 L	(+) Biopsy; (+) Aspirate**	
V6 08JUL2003	10.3 L	4.9	181		PR
V9 02SEP2003*	12.0	7.6	182		
V17 06JUL2004	11.9	5.4	173		

L=value under lower limit of normal range; H=value above upper limit of normal range; V=visit; PR=partial response

* CBC normalized; ** Eosinophils 12%

[a] Source: [Study B2225–PTL **7.1 Listing 1.21** from page 3921/3943 to page 3943/3943]

[b] Source: [Study B2225–PTL **7.1 Listing 1.21** from page 3921/3943 to page 3943/3943]

[c] Source: [Study B2225–PTL **7.1 Listing 1.21** from page 3921/3943 to page 3943/3943]

[d] Source: [Study B2225–PTL **7.1 Listing 1.4** from page 8/9 to page 9/9]

[e] Source: [Study B2225–PTL **7.1 Listing 1.14** from page 30/31 to page 31/31]

Investigator comments relevant to bone marrow and response assessments – Study B2225, Patient ——'901/177: b(6)

Visit 15, 06APR2004	ASSESSMENTS NOT DONE THIS VISIT BY ——. ALL WORKUP-BONE MARROW BIOPSY + ULTRASOUND TO BE DONE IN MAY 04 – JUST PRIOR TO APHERSIS
Visit 16, 25MAY 2004	ABDO US SHOWS MILD SPLENOMEGALY, SHOWING REDUCING FROM EARLIER STUDIES. 2/9/2003 13.8CM 25/11/2003 12.8CM 25/5/2004 11.8CM. BONE MARROW ASPIRATE 25/5/04 SHOWS MILD EOSINOPHILIA (5%) WITH HYPOGRANULAR FORMS CONSISTENT WITH MINIMAL RESIDUAL DISEASE. GOOD ONGOING RESPONSE
Source:	[Study B2225–PTL **7.1 Listing 1.22** from page 131/132 to page 132/132]

Staten, Ann M

From: robert.miranda@novartis.com
Sent: Friday, January 13, 2006 3:51 PM
To: Staten, Ann M
Cc: 'joseph.quintavalla@novartis.com'
Subject: Re: FW: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Ann,

Sorry for any misunderstandings. I have spoken with the clinical and biostat persons (they are in Switzerland) and I can clarify one of your two comments as follows:

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Novartis Clarification:

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To: Robert Miranda/PH/Novartis@PH
cc: Joseph Quintavalla/PH/Novartis@PH

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Please clarify.

Thanks,
Ann

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Sent: Thursday, January 12, 2006 12:53 PM
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Subject: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

Dear Ann,

The following response is made to your information request of 1/5/06:

FDA Reviewer's Question

"We are having a hard time confirming responses of the 7 MDS/MPD patients in study B2225 using the submitted datasets. Please provide serial hematology and bone marrow data for each of the 7 patients."

Novartis Reply

The derived datasets which contain all the relevant tumor evaluation information are the following

"A_TUM.sas": Assessment of Tumor Response
"A_TUMD.sas": Tumor description
"A_TUMA.sas": Tumor Assessment
"A_TUMC.sas": Tumor Assessment Comments

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this listing.

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This tabulates descriptive summary indices of hematology parameters by visit and by malignancy type.

I hope this is helpful. Please let me know if you have any questions or comments. A formal copy of this response will be sent to the NDA.

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Bob.....

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Robert A. Miranda, R.A.C.
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Assistant: [redacted] b(6)
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"Staten, Ann M" <STATENA@cder.fda.gov>

01/05/2006 12:17 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: information request - NDA 21-588/S-

Dear Bob,

- We have the following request from the medical reviewer for the MDS/MPD supplement (S-012).

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- Please provide serial hematology and bone marrow data for each of the 7 patients.

- Sincerely,

- Ann

- P.S. DFSP was assigned S-011 and ALL was assigned S-013

Staten, Ann M

From: robert.miranda@novartis.com
Sent: Thursday, January 12, 2006 12:53 PM
To: Staten, Ann M
Cc: joseph.quintavalla@novartis.com
Subject: Gleevec: Information Request #1 - NDA 21-588/S-012 (MDS/MPD Indication)

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FDA Reviewer's Question

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"A_TUMD.sas": Tumor description
"A_TUMA.sas": Tumor Assessment
"A_TUMC.sas": Tumor Assessment Comments

These datasets are included in the Case Report Tabulations, as well as the description of variables (Item 11 in this sNDA).

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  This lists, by MPD/MDS patients, all the assessments of tumor response per visit along with the date of assessment and the actual study day. Post-Text Table 9.1-1 is derived from the information contained in this listing.

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  This tabulates the assessment of tumor response by visit and provides as well the tabulation of the best overall response. Note that the assessment at each evaluation is based on investigator's evaluation of the objective tumor status and not on recalculated response.

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This lists, by MDS/MPD patients, the Lab Biochemistry test results by parameter. Also contained in this listing is the more important hematology test results for MDS/MPD patients (page 3807).

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This tabulates descriptive summary indices of hematology parameters by visit and by malignancy type.

I hope this is helpful. Please let me know if you have any questions or comments. A formal copy of this response will be sent to the NDA.

Thanks,
Bob.....

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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
Assistant: [redacted] b(6)
****

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

01/05/2006 12:17 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: information request - NDA 21-588/S-0

Dear Bob,

We have the following request from the medical reviewer for the MDS/MPD supplement (S-012).

We are having a hard time confirming responses of the 7 MDS/MPD patients in study B2225 using the submitted datasets.

Please provide serial hematology and bone marrow data for each of the 7 patients.

Sincerely,

Ann

P.S. DFSP was assigned S-011 and ALL was assigned S-013

Staten, Ann M

From: robert.miranda@novartis.com
Sent: Thursday, January 12, 2006 12:51 PM
To: Staten, Ann M
Cc: joseph.quintavalla@novartis.com
Subject: Gleevec: Information Request #2 for NDA 21-588/S-012 (DFSP Indication)

Dear Ann,

The following response is made to your information request of 1/5/06:

FDA Reviewer's Question

"We are having a hard time confirming responses of the 12 dematofibrosarcoma protuberans patients in study B2225 using the submitted datasets. Please provide serial tumor measurement data for each of the 7 [I believe you meant 12] patients."

Novartis Reply

The derived datasets which contain all the relevant tumor evaluation information are the following

"A_TUM.sas": Assessment of Tumor Response
"A_TUMD.sas": Tumor description
"A_TUMA.sas": Tumor Assessment
"A_TUMC.sas": Tumor Assessment Comments

These datasets are included in the Case Report Tabulations, as well as the description of variables (Item 11 in this sNDA).

Please consider the following patient data listings and post-text tables (Appendix 7 and Supplement 3, respectively, of the Clinical Study Report for B2225 in Item 8 of this sNDA) carried out using the above data.

- **Appendix 7.1 Listing 1-14: Response Assessment, by Visit, Indication and Malignancy Type (pages 595 of Appendix 7)**

  This lists, by DFSP patients, all the assessments of tumor response per visit along with the date of assessment and the actual study day. Post-Text Table 9.1-1 is derived from such information.

-
  - **Post-Text Table 9.1-1: Assessment of Tumor Response, by Visit, Indication and Malignancy Type (page 1053 of Supplement 3)**

    This tabulates the assessment of tumor response by visit and provides as well the tabulation of the best overall response. Note that the assessment at each evaluation is based on investigator's evaluation of the objective tumor status and not on recalculated response.
  - **Appendix 7.1 Listing 1-15: Tumor Descriptions, by Indication and Malignancy Type**

(pages 625 of Appendix 7)

This lists all tumor descriptions by DFSP patient.

- **Appendix 7.1 Listing 1-16: Tumor Assessments, by Indication and Malignancy Type (pages 675 of Appendix 7)**

This lists, by DFSP patient, all tumor assessments per lesion with the corresponding measurements.

- **Appendix 7.1 Listing 1-17: Tumor Assessment Comments, by Visit, Indication and Malignancy Type (pages 734 of Appendix 7)**

This lists all tumor assessment comments by DFSP patient.

I hope this is helpful. Please let me know if you have any questions or comments. A formal copy of this response will be sent to the NDA.

Thanks,
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
Assistant: [redacted] b(6)

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

01/05/2006 12:55 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: information request for NDA 2

Dear Bob,

Here is another information request from the medical reviewer:

We are having a hard time confirming responses of the 12 dematofibrosarcoma

protuberans patients in study B2225 using the submitted datasets.

Please provide serial tumor measurement data for each of the 7 patients.

Sincerely,

Ann

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office			FROM:	
/MAC, HFD-42			Ann Staten	
DATE 1-6-06	IND NO.	NDA NO. 21-588/S-011, 012, 013	TYPE OF DOCUMENT New sNDAs	DATE OF DOCUMENT 12-16-05x2 and 12-21-05
DRUG Gleevec (imatinib mesylate)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER (fax)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: We have 3 new sNDAs in the EDR. Marty Cohen is the medical reviewer. The submissions in the EDR are S-011, 012 and 013.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Ann Staten	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Ann Staten
1/6/2006 10:37:31 AM

NOVARTIS
ONCOLOGY

December 20, 2005

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsvillle, MD 20705-1266

No. 21-588

GLEEVEC ® (imatinib mesylate) tablets

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

(NEW INDICATION: Ph+ ALL)

Dear Dr. Justice:

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate) approved for the treatment of patients with Philadelphia chromosome (Ph+) chronic myeloid leukemia, and with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

At this time Novartis Pharmaceuticals Corporation is submitting a supplemental New Drug Application (sNDA) for the use of Gleevec [redacted] b(4) as a single agent for the treatment of adult patients with relapsed or refractory Ph+ ALL. SO183

This sNDA consists of essential data from Novartis studies 03001, 0109 & 0114, and additional data from publications in peer reviewed journals as agreed in a Type B meeting on January 10, 2005.

The studies in Ph+ ALL can be divided into those using

- Gleevec in combination with induction and/or consolidation chemotherapy in newly diagnosed patients (n=315),
- Gleevec as monotherapy or in combination with chemotherapy in relapsed/refractory patients (n=443).

In addition, the efficacy and safety of Gleevec was evaluated in patients aged 55 years or more (elderly) who are conventionally considered as not amenable to curative treatment with bone marrow transplantation (n=250 from above referenced studies).

Request for Priority Review

Gleevec is intended for the treatment of patients with Ph+ ALL ——————— b(4) and in relapsed/refractory patients. These are medical conditions that are rare (orphan designation No. 05-2089, October 11, 2005), and for which there is a clear unmet medical need. The clinical data demonstrate that Gleevec provides a clinical benefit, in complete response rate and duration, disease-free survival and/or overall survival when compared to the historical controls. It is therefore important to integrate this new indication in the product labeling as recommended, in order to offer patients with these conditions an effective alternative to the existing treatments. Gleevec is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis. Given this profile and the innovative, rational and well understood mechanism of action, Novartis believes that this application qualifies for priority review according to CDER's MAPP 6020.3, in that Gleevec offers a significant improvement in the treatment of Ph+ ALL, a serious and life-threatening condition, compared to available historical therapies.

We believe that this application will entitle Gleevec to a 5 year period of exclusivity based on the new data from the Novartis studies that are essential to approval of this supplement and support for the indication.

The Gleevec formulation is the same as previously approved for CML and GIST, and therefore, there is no preclinical or technical information in this sNDA. There are no changes to the chemistry, non-clinical pharmacology, toxicology, human pharmacokinetics and bioavailability sections. The CMC section is limited to an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of section 3 is being provided to our district office.

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – Content of Labeling (*April 2005). The relevant technical details of the electronic portions of this submission are as follows:

• **Submission size:**	approximately 274 MB
• **Electronic media:**	one compact disc
• **Virus scan:**	Network Associates Incorporated VirusScan© version 7.1.0 (formerly known as the McAfee VirusScan). The submission is virus free.

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

If you have any questions or comments, please contact me at 862-778-0233.

Sincerely,

Robert Miranda
for Joseph Quintavalla
Senior TA Manager
Drug Regulatory Affairs

NOVARTIS
ONCOLOGY

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

December 16, 2005

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

No. 21-588

GLEEVEC ® (imatinib mesylate) tablets

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

(NEW INDICATION: MDS/MPD)

Dear Dr. Justice:

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate) approved for the treatment of patients with Philadelphia chromosome chronic myeloid leukemia, and with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

At this time Novartis Pharmaceuticals Corporation is submitting a supplemental New Drug Application (sNDA) for the use of Gleevec in a new indication for the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. This sNDA consists of essential data from a Novartis Phase II study B2225 and additional data from publications in peer reviewed journals as agreed upon in a Type B meeting on August 12, 2004. Four rare diseases (including MDS/MPD) were addressed at that meeting, and were investigated in study B2225. At the request of the FDA, (Ann Staten/Robert Miranda telcon of July 21, 2005) each of the four rare disease indications are being submitted separately.

Request for Priority Review

Gleevec is intended for the treatment of patients with MDS/MPD associated with PDGFR gene re-arrangements. These are medical conditions that are very rare (Orphan designation No. 05-2091, October 5, 2005), and for which there is a clear unmet medical need. The clinical data demonstrate that Gleevec provides very high complete hematologic and cytogenetic responses that are higher than that obtained with any other drug therapy used. These clinical results allowed patients to be maintained on Gleevec up to 18 months or longer, with all responding patients still on treatment or had moved to a bone marrow transplant (the only known potential curative treatment). Gleevec is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis. Given this profile and the innovative, rational and well understood mechanism of action, Novartis believes that this application qualifies for priority review according to CDER's MAPP

6020.3, in that Gleevec offers a significant improvement in the treatment of MDS/MPD associated with PDGFR gene re-arrangements, a serious and life-threatening condition, compared to available historical therapies.

We believe that this application will entitle Gleevec to a 5 year period of exclusivity based on the new data from the Novartis study (B2225) that are essential to approval of this supplement and support for the indication.

The Gleevec formulation is the same as previously approved for CML and GIST, and therefore, there is no preclinical or technical information in this sNDA. There are no changes to the chemistry, non-clinical pharmacology, toxicology, human pharmacokinetics and bioavailability sections. The CMC section is limited to an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of section 3 is being provided to our district office.

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If you have any questions or comments, please contact me at 862-778-0233.

Sincerely,

for Joseph Quintavalla
Senior TA Manager
Drug Regulatory Affairs

NOVARTIS
ONCOLOGY

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

December 16, 2005

Robert L. Justice, MD
Acting Director
Food and Drug Administration
Center of Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsvillle, MD 20705-1266

No. 21-588

GLEEVEC ® (imatinib mesylate) tablets

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

(NEW INDICATION: DFSP)

Dear Dr. Justice:

Reference is made to our NDA 21-588 for Gleevec® (imatinib mesylate) approved for the treatment of patients with Philadelphia chromosome chronic myeloid leukemia, and with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

At this time Novartis Pharmaceuticals Corporation is submitting a supplemental New Drug Application (sNDA) for the use of Gleevec in a new indication for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP). This sNDA consists of essential data from a Novartis Phase II study B2225 and additional data from publications in peer reviewed journals as agreed upon in a Type B meeting on August 12, 2004. Four rare diseases (including DFSP) were addressed at that meeting, and were investigated in study B2225. At the request of the FDA, (Ann Staten/Robert Miranda telcon of July 21, 2005) each of the four rare disease indications are being submitted separately.

Request for Priority Review

Gleevec is intended for the treatment of patients with DFSP. This is a medical condition that is very rare (orphan application No. 05-2088, dated July 8, 2005 under review), and for which there is a clear unmet medical need. The clinical data demonstrate that Gleevec provides high response rates that are higher than that obtained with other drug therapy used. Overall response rate of 83% was observed in the population of patients with DFSP in Study B2225, and a 62% response rate was observed in patients with metastatic disease in the literature. Median duration of therapy was 140 days (maximum 685 days) in Study B2225. Surgical resection was made possible after partial response to imatinib treatment in five patients, which lead to a complete cure of the disease.

It is therefore important to integrate this new indication in the product labeling as suggested, in order to offer patients with this condition an effective alternative to the existing chemotherapy treatment and in some cases the possibility of cure by surgery. Gleevec is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis. Given this profile and the innovative, rational and well understood mechanism of action, Novartis believes that this application qualifies for priority review according to CDER's MAPP 6020.3, in that Gleevec offers a significant improvement in the treatment of DFSP, a serious and life-threatening condition, compared to available historical therapies.

We believe that this application will entitle Gleevec to a 5 year period of exclusivity based on the new data from the Novartis study (B2225) that are essential to approval of this supplement and support for the indication.

The Gleevec formulation is the same as previously approved for CML and GIST, and therefore, there is no preclinical or technical information in this sNDA. There are no changes to the chemistry, non-clinical pharmacology, toxicology, human pharmacokinetics and bioavailability sections. The CMC section is limited to an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of section 3 is being provided to our district office.

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• **Submission size:**	approximately 175 MB
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Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent

If you have any questions or comments, please contact me at 862-778-0233.

Sincerely,

for Joseph Quintavalla
Senior TA Manager
Drug Regulatory Affairs

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

06/30/2005 11:03 AM

To: Robert Miranda/PH/Novartis@PH, "Staten, Ann M" <STATEN
cc: Joseph Quintavalla/PH/Novartis@PH
Subject: RE: Gleevec - Heads up on 2 new filings planned

Dear Bob,

We have looked at the two proposals below for the expected sNDA submissions and we agree with both.

Sincerely,
Ann

-----Original Message-----
From: robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]
Sent: Wednesday, June 22, 2005 1:40 PM
To: statena@cder.fda.gov
Cc: joseph.quintavalla@novartis.com
Subject: Gleevec - Heads up on 2 new filings planned

Hi Ann,

FYI, Novartis is planning to submit sNDA submissions for new indications for Gleevec on the following dates: b(4)

- September 30, 2005: Rare Diseases (DFSP, HES, — , MPD/MDS - EOP1 Meeting 8/12/04)
- November 15, 2005: Ph+ ALL (EOP1 Meeting 1/10/05)

These sNDAs will contain clinical data only. All other information will be unchanged and cross-referenced to tl original NDA (e.g. CMC, Preclinical, Clinical Pharmacology) similar to the past sNDA for newly diagnosed CMl

In preparing for these submission we have the following two short questions:

1. For each submission we propose to submit patient narratives only for the following serious adverse events (SAEs):
   - Deaths not due to progressive disease
   - Discontinuations for treatment-related adverse events
   - All trial drug-related SAEs

2. For each submission can we provide Case Report Forms only upon request?

We do not anticipate any further questions or the need for a pre-NDA meeting if we can resolve these two questions.

Thanks again for your continuing support and assistance.

Much appreciated,
Bob.....

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

NOVARTIS PHARMACEUTICALS CORP
Angie Young
One Health Plaza
East Hanover NJ 07936
US

2. TELEPHONE NUMBER
862-778-8685

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-588

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Gleevec (Imatinib mesylate)

6. USER FEE I.D. NUMBER
PD3006358

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Vera Ne	Director	12/8/05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$383,700.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

TELECOM MEETING MINUTES

MEETING DATE: January 10, 2005

IND/NDA: IND 55,666 **Meeting Request Sub. Date:** November 19, 2004 (N694)
FDA Response Date: November 30, 2004
Briefing Document Submission Date: November 19, 2004 (N694)

DRUG: Gleevec (imatinib mesylate)

SPONSOR/APPLICANT: Novartis

TYPE of MEETING/TELECON:

1. pre-sNDA

2. Proposed Indication: adult Ph+ ALL

FDA PARTICIPANTS:
Richard Pazdur, MD, Director, DODP
John Johnson, MD, Medical Team Leader
Martin Cohen, MD, Medical Reviewer
Rajeshwari Sridhara, PhD, Statistics Team Leader
Sophia Abrraham, PhD, Clinical Pharmacology Reviewer
Ann Staten, RD, Project Manager

INDUSTRY PARTICIPANTS: Robert Miranda, Director, Drug Regulatory Affairs

BACKGROUND: Following the January 6, 2005 FDA internal meeting, responses to Novartis questions were sent via e-mail on January 6, 2005. On January 10, 2005, Robert Miranda informed the Agency that a meeting was no longer necessary (see attached e-mail) and cancelled the meeting.

MEETING/TELECON OBJECTIVES: To reach agreement that the current studies conducted by Novartis and other investigators are sufficieint to support filing an efficacy supplement.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

See attached.

There were no unresolved issues or action items.

Concurrence Chair:

Ann Staten, RD
Project Manager

John Johnson, MD
Medical Team Leader

Attachments: Novartis email dated 1-10-05; FDA email dated 1-6-05; Novartis overall development plan and protocol outlines

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Monday, January 10, 2005 3:06 PM
To: Staten, Ann M
Subject: Re: IND 55,666 (Serial No. 694) - pre-sNDA meeting Ph+ ALL

Hi Ann,

This is to notify you that we would like to cancel the meeting scheduled for 1/12/05. I also want to thank you and your team for your review of our proposal, and for the advance distribution of the answers to our questions. This is very efficient and helpful.

Best regards,
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
Assistant: [redacted] b(6)
****

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

01/06/2005 01:36 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: IND 55,666 (Serial No. 694) - pre-sNDA meeting Ph+ ALL

Dear Bob,

Attached are the FDA answers to your questions and our standard pre-sNDA comments. You have the

option of canceling our meeting of January 12, 2005if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Sincerely,

Ann

[Attachment "NOVARTIS QUESTIONS FOR 1-6-05 PRE-MTG.DOC" removed by Robert Miranda]
[Attachment "PRE-NDA MEETING BULLETS.DOC" removed by Robert Miranda]

1/21/2005

Novartis questions

Required clinical data to obtain line extension within the indication of Ph+ALL

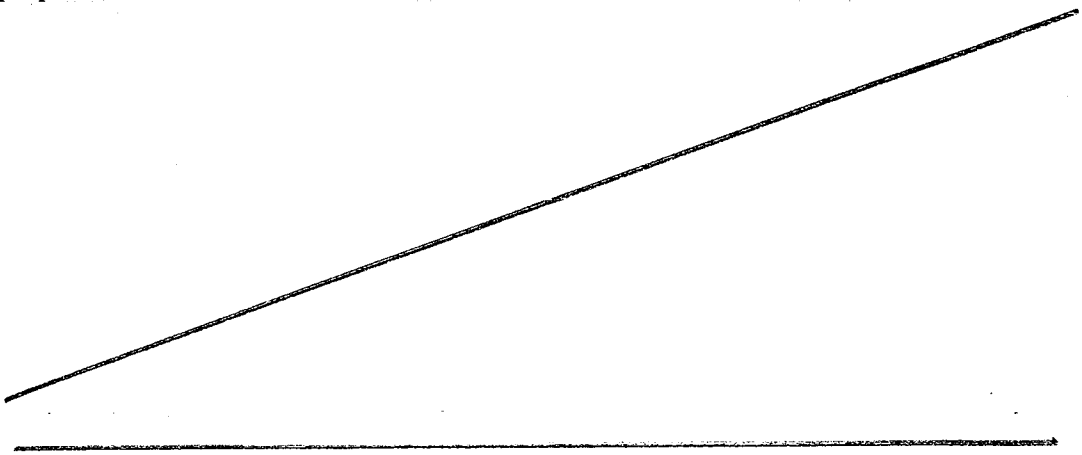
The new indication of Ph+ALL described in this briefing book is a rare malignancy of unmet medical need in an orphan indication for which Novartis will file an Orphan Drug Application based on prevalence criteria. The indication being sought is:

Gleevec® is indicated in the treatment of adult patients with Ph+ALL, —— as single agent ——————→ b(4)

The corresponding clinical data package for obtaining this line extension will include full clinical trial reports and data from the Novartis phase I study (study number 03001), the Novartis Phase II study (study number 0109) and the Novartis phase II expanded access study (study number 0114) as well as publications in peer review journals for the completed non-Novartis sponsored trials.

Company position:

In the relapsed and/or refractory patient population a complete hematological response rate of 30% was achieved after treatment with Gleevec used as a single agent. In this patient population deprived of any other therapeutic options no further studies will be proposed.



b(4)

——————— . Monotherapy induction with Gleevec is associated with a similar or higher complete response rate (77% to 100%) but no toxic deaths were reported (table 4-13). Given the high risk of toxic deaths in any possible control arm, a direct comparison of imatinib mesylate with conventional chemotherapy may not be appropriate.

At the time of registration the clinical registration package will encompass over 600 patients with a safety database of at least 631 patients and an efficacy database of at least 336 patients (table 5-1). The toxicity profile of imatinib mesylate used as a single agent in patients with Ph+ALL (n=485) was very similar to what was observed in patients with

Ph+CML. Furthermore, the safety profile of imatinib mesylate used in combination with chemotherapies in patients with Ph+ALL (n=146) was similar to that seen in combination chemotherapies alone. Therefore, we believe that the safety profile of imatinib mesylate in Ph+ALL patients is adequately addressed.

Efficacy data are available for 336 patients with Ph+ALL (included in 12 open-label clinical studies, one being a randomised trial). Six studies were performed with Gleevec used as a single agent and six additional studies were conducted with Gleevec used in combination with chemotherapies (section 5). Therefore, we consider the efficacy data being investigated sufficiently.

Results of the ongoing trials (study numbers AFR09, AIT04, AFR03, AES02, AJP01, AUS01, AAU02) which are referenced in this briefing book as abstracts will be made available as peer-reviewed publications and will be part of the clinical registration package at the time of submission.

1. Does the agency concur with this approach?

FDA Response: Yes

Dose regimen for Ph+ALL

Novartis is proposing a starting dose of imatinib mesylate of 600 mg / day — used as a single agent ——————————

b(4)

Company position:

This posology was administered in most of the clinical trials discussed in this briefing book.

Up to now 239 (71%) of 336 patients with efficacy data available received a dose of 600 mg / day :

- 97 refractory and/or relapsed patients treated in monotherapy with Gleevec in Novartis sponsored trials (Table 4-4)

- 98 newly diagnosed patients treated with Gleevec in combination with chemotherapy (Table 4-8 and Table 4-10)

- 38 elderly patients treated in monotherapy induction with Gleevec (Table 4-6)

- 6 relapsed patients treated with Gleevec in combination with chemotherapy (Table 4-10)

With regard to safety, currently 543 (86%) of 631 patients received a dose of 600 mg / day (Table 4-12; Table 4-13 and Table 4-14)

The 600 mg dose per day was found to be effective and safe. In addition, 600 mg / day is the applied posology in the already registered indication of CML in lymphoid blast crisis which is biologically similar to Ph+ALL.

2. Is this acceptable?

FDA Response: Yes, we agree that you should submit the data using 600mg. Safety and efficacy of the 600 mg dose in the various populations will be a review issue.

Additional comment: 38 elderly patients treated with Gleevec is a rather small data base for support of the use of Gleevec as monotherapy in this population.

OTHER FDA COMMENTS:

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Gleevec®

Overall Development Plan

Indication:

For the treatment of adult patients with Philadelphia-positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Proposed pivotal trial(s):

1. **Clinical Phase I Study No. 03001**
2. **Clinical Phase II Study No. 0109**
3. **Expanded Access Study No. 0114**
   (includes 14 patients from Study No. 0109)

Proposed supportive trial(s):

1. **Non-Novartis sponsored clinical trials published in peer reviewed journals**

Protocol Outline

Protocol number/title: Study No. CSTI571 03001

Title: A phase I, dose finding, study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles, and to evaluate for preliminary anti-leukemic effects of CGP571 48B (Imatinib) in patients with CML who are resistant or intolerant of IFNα.

Objective(s):

Primary: a) To assess the safety and tolerability, and to establish the maximum tolerated dose of Imatinib when administered orally to Ph chromosome-positive CML patients in chronic phase who are resistant to or intolerant of IFNα.
b) To obtain PK profiles at different escalating doses.

Secondary: a) To obtain preliminary evidence of anti-leukemic activity as shown by a decrease in peripheral white blood cell counts and the percentage of Ph chromosome-positive cells in the bone marrow.
b) To obtain preliminary evidence of inhibition of TK activity of the chimeric bcr-abl protein using a phosphotyrosine immunoblot assay.

Design:

This was a pilot dose-escalation study. Patients were assigned to successive dose cohorts of STI571 ranging from 300 to 1000 mg.

Patient Population:

- Male or female patients at least 18 years of age
- A total of 58 patients were treated; 38 patients had myeloid blast crisis and 20 had ALL or lymphoid blast crisis.

Dosing plan / treatment plan / schema:

Successive oral dose cohorts of STI571 ranging from 300 to 1000 mg, 6 to 8 patients for each dose.
STI571 doses of 800 mg and 1000 mg were administered twice daily in 400-mg and 500-mg doses
respectively.

Efficacy Endpoints:

Primary
The primary efficacy endpoints were hematologic and cytogenetic responses assessed as: Complete hematologic response (CHR), complete marrow-response (marrow-CR), relapse, cytogenetic response (complete, partial, minor, absent).

Secondary
Safety assessments

Definition of Endpoints:

- **Complete hematologic response (CHR),** defined as follows maintained for at least four weeks:

Decrease in marrow blasts to 5% or less of total cellularity, Disappearance of blasts from the peripheral blood

Absolute neutrophil count of more than 1000 per cubic millimeter

- **Marrow response (marrow-CR)** defined as decrease in marrow blasts to either no more than 5% or between 5 to 15%, regardless of the peripheral-blood cell counts.

- **Relapse**, defined as either disease progression (an increase in marrow blasts to more than 15%, in peripheral-blood blasts to more than 5% or white cells to more than 20,000 per cubic millimeter) or death.

Time to relapse was calculated from the first dose of STI571

- **Cytogenetic responses** based on analysis of 20 cells in metaphase, were characterized as:

Complete (no cells positive for Ph chromosome)

Partial (1 to 35 % of cells positive for Ph chromosome)

Minor (35 to 65% of cells positive for Ph chromosome)

Absent (over 65% of cells positive for Ph chromosome)

Safety Monitoring:

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, patient interview at each office visit and performance of physical examinations and documentation of all concomitant medication and therapies.

Statistical Plan:

Sample size/basis: A total of 58 patients were enrolled, 38 patients had myeloid blast crisis and 20 had lymphoid blast crisis or ALL. Overall rates of response were 55% and 70% among patients with myeloid and lymphoid blast crises respectively / Completed and statistically valid.

Analyses: In the intention-to-treat analysis of response rates, all patients in the study were included whether or not the response could be properly evaluated.

Estimated start and completion dates:

First patient enrolled: April 1999

Study currently completed with report dated September 2, 2004

Protocol Outline

Protocol number/title: Study No. CSTI571 0109

Title: A phase II study to determine the anti-leukemic effects of STI571 in adult patients with Ph+ leukemia including ALL, AML, CML-LBC and accelerated phase CML.

Objective(s):

Primary: To evaluate clinical efficacy of imatinib as determined by the rate of sustained hematologic response (lasting at least 4 weeks), and the safety of treatment in patients with relapsed or refractory Ph+ ALL (Philadelphia chromosome-positive acute lymphoid leukemia).

Secondary: To evaluate time to disease progression, overall survival and induction of cytogenetic response.

Design:

This was an open label, nonrandomized, multicenter, multinational Novartis sponsored phase 2 trial treated with imatinib at daily doses of 400 or 600 mg.

Patient Population:

- Male or female patients at least 18 years of age
- Confirmed diagnosis of relapsed or refractory Ph+ ALL or LyBC

Dosing plan / treatment plan / schema:

Patients started treatment with imatinib at daily doses of 400 or 600 mg for 24 weeks and continued indefinitely in cases where the investigator judged that further treatment was of clinical benefit.

Efficacy Endpoints:

Primary: The primary efficacy endpoint was sustained hematologic response lasting at lest 4 weeks observed at 2 consecutive evaluations, assessed as Complete hematologic response (CHR), Complete marrow response (marrow-CR) or partial response (PR).

Secondary: Induction of a Complete cytogenetic response, Time to disease progression (TTP) or Overall survival (OS)

Definition of Endpoints:

CHR: blast count below 5% in bone marrow, no blasts in peripheral blood, neutrophil count at least 1.5 x 10^9/L, platelet count at least 100 x 10^9/L, and no evidence of extramedullary involvement

Marrow-CR: blast count of less than 5% in bone marrow, no blasts in peripheral blood, no evidence of extramedullary involvement, a neutrophil count at least 1.0 x 10^9/L, but no platelet recovery (platelet count at least 20 x 10^9/L)

PR: Less than 15% blasts in peripheral blood and bone marrow.

CCR: the absence of Ph+ metaphases in bone marrow

TTP: the time from treatment start until relapse after initial response, or the interval when the treatment was discontinued owing to unsatisfactory therapeutic response, adverse events, or patient death.

OS: the time from treatment start to the date of death from any cause.

Safety Monitoring:

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, patient interview at each office visit and performance of physical examinations and documentation of all concomitant medication and therapies.

Statistical Plan:

Sample size/basis: 56 patients at 18 centers / Completed and statistically valid.

Analyses: Response rates were reported as intent-to treat analyses. Patients who withdrew from treatment before a sustained response were counted as non-responders. Time to progression and survival were computed by means of standard Kaplan-Meier methods.

Estimated start and completion dates:

First patient enrolled: September 1, 1999

Study currently completed with report dated July 15, 2004

Protocol Outline

Protocol number/title: Study No. CSTI571 0114

Title: An expanded-access study of glivec® in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia

(includes 14 patients from study 0109)

Objective(s):

Primary: To assess the prognostic impact of pretreatment disease features and the early bone marrow (BM) response in patients with Ph+ ALL receiving imatinib salvage therapy.

Secondary: To evaluate time to disease progression, overall survival and induction of cytogenetic response.

Design:

This was an open label, nonrandomized, multicenter, expanded access Novartis sponsored phase II trial treated with imatinib at daily doses of 300, 400 or 600 mg.

Patient Population:

- Male or female patients at least 18 years of age
- Confirmed diagnosis of relapsed or refractory Ph+ ALL or LyBC

Dosing plan / treatment plan / schema:

Patients started treatment with imatinib at daily doses of 300, 400 or 600 mg for 24 weeks and continued indefinitely in cases where the investigator judged that further treatment was of clinical benefit.

Efficacy Endpoints:

Primary: The primary efficacy endpoint was sustained hematologic response lasting at lest 4 weeks observed at 2 consecutive evaluations, assessed as Complete hematologic response (CHR), Complete marrow response (marrow-CR) or partial response (PR).

Secondary: Induction of a Complete cytogenetic response, Time to disease progression (TTP) or Overall survival (OS)

Definition of Endpoints:

CHR: blast count below 5% in bone marrow, no blasts in peripheral blood, neutrophil count at least 1.5 x 10^9/L, platelet count at least 100 x 10^9/L, and no evidence of extramedullary involvement

Marrow-CR: blast count of less than 5% in bone marrow, no blasts in peripheral blood, no evidence of extramedullary involvement, a neutrophil count at least 1.0 x 10^9/L, but no platelet recovery (platelet count at least 20 x 10^9/L)

PR: Less than 15% blasts in peripheral blood and bone marrow.

CCR: the absence of Ph+ metaphases in bone marrow

TTP: the time from treatment start until relapse after initial response, or the interval when the treatment was discontinued owing to unsatisfactory therapeutic response, adverse events, or patient death).

OS: the time from treatment start to the date of death from any cause.

Safety Monitoring:

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, patient interview at each office visit and performance of physical examinations and documentation of all concomitant medication and therapies.

Statistical Plan:

Sample size/basis: A total of 68 patients were enrolled with relapsed or refractory Ph+ ALL (n=66) or minimal residual disease (n=2) / Completed and statistically valid.

Analyses:

Kaplan-Meier analysis and log rank test were performed using the GraphPad Prism software package.
For Time to progression (TTP) analysis, patients undergoing SCT were censored at the time of transplantation. The Fisher exact test (2-sided) was performed using BIAS statistical software program.

Estimated start and completion dates:

First patient enrolled: August 1, 1999

Study currently completed with report dated July 16, 2004

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

/s/

Ann Staten
1/26/05 10:10:43 AM

John Johnson
1/26/05 11:21:50 AM

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, August 17, 2004 1:34 PM
To: 'robert.miranda@pharma.novartis.com'
Subject: RE: IND 55,666 mtg request - rare diseases

Dear Bob,

The comment that was made to correlate drug PK to biomarkers and endpoints of effectiveness and safety is generally applicable in drug development. In this particular case, the remarks were made with respect to the B2225 study. However, they can be applied to Gleevec in general, and if you are exploring other data, you could try these correlations for that (those) study(ies) as well.

Sincerely,
Ann

-----Original Message-----
From: robert.miranda@pharma.novartis.com [mailto:robert.miranda@pharma.novartis.com]
Sent: Friday, August 13, 2004 12:01 PM
To: Staten, Ann M
Subject: Re: IND 55,666 mtg request - rare diseases

Hi Ann,

Can you clarify that the Clinical Pharmacology Comment relates only to the Novartis study B2225?

Thanks
Bob.....

Robert A. Miranda
Drug Regulatory Affairs
Novartis Oncology

phone: +862-778-2282
fax: +973-781-5217

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

08/13/2004 10:45 AM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: IND 55,666 mtg request - rare diseaes

Dear Bob,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of August 18, 2004if these answers are clear to you. If you choose to have the meeting, we will be prepared to

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

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)

[Attachment "MTG QUESTIONS RARE DISEASES.DOC" removed by Robert Miranda]
[Attachment "EOP2 MEETING BULLETS.DOC" removed by Robert Miranda]

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

/s/

Ann Staten
9/1/04 09:34:42 AM

John Johnson
9/1/04 10:16:03 AM

MEETING MINUTES

MEETING DATE: August 12, 2004

IND/NDA IND 55,666 Meeting Request Submission Date: June 29, 2004 (N649)
Briefing Document Submission Date: June 29, 2004 (N649)

DRUG: Gleevec (imatinib mesylate)

SPONSOR/APPLICANT: Novartis

TYPE of MEETING:

1. **EOP1-2**

FDA PARTICIPANTS:
Robert Temple, MD, Director, Office of Drug Evaluation 1
Richard Pazdur, M.D., Director, Division of Oncology Drug Products
John Johnson, MD, Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
Angela Menn, PhD, Clinical Pharmacology Reviewer
Raji Sridhara, PhD, Acting Statistical Team Leader
Ann Staten, RD, Project Manager

MEETING OBJECTIVES:

To discuss the sNDA submission of Gleevec for very rare diseases [Dermatofibrosarcoma protuberans (DFSP), Hypereosinophilic syndrome (HES), [redacted] b(4) Myeloproliferative disorders (MPD) and Myelodysplastic syndromes (MDS) associated with activating mutations involving the PDGFR gene].

BACKGROUND: Following the internal pre-meeting on 8-12-04, FDA's responses were sent to the sponsor in an e-mail dated 8-12-04 (attached). On 8-13-04, Novartis requested clarification regarding the clinical pharmacology comment. On 8-16-04, the sponsor requested that the meeting be cancelled. On 8-18-04, FDA responded to the 8-13-04 request for clarification of the clinical pharmacology comment (see attached).

ACTION ITEMS:

There were no unresolved issues or discussion points.

_____ /_____
Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: _____ /_____
John Johnson, M.D. Date
Medical Team Leader

Staten, Ann M

From: Staten, Ann M
Sent: Friday, August 13, 2004 10:45 AM
To: 'robert.miranda@pharma.novartis.com'
Subject: IND 55,666 mtg request - rare diseaes

Dear Bob,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of August 18, 2004 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

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)

8/24/2004

1. The new indications being sought are rare malignancies with unmet medical need. All the efficacy and safety data Novartis plans to submit are publications in peer reviewed journals (for which we have no access to additional data). In addition, data from a Novartis Phase II trial will be provided. Based on the industry guidance "FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products", and given the rarity of the diseases being considered including the unmet medical need, we believe this is adequate for registration.

   Do you agree?

   FDA Response: Why is there uniformly no access to primary data from the published studies?

   The quality of the publications could determine the need for such data.

   Of concern is the certainty of pathologists in making the diagnosis of these rare diseases. For example, what would be the concordance among pathologists in diagnosing dermatofibrosarcoma protuberans (DFSP)? Is it necessary to demonstrate characteristic cytogenetic abnormalities? For hypereosinophilic syndrome how readily available is the test for the fusion gene product FIP1L1/PDGFRa? Does c-kit mutation have to be demonstrated in mast cell diseases?

   We may also want to be able to confirm the claimed responses.

2. Our proposal involves extremely rare diseases with unmet medical needs, for which Gleevec-sensitive targets have been identified as a key pathological cause while at the same time a very high degree of efficacy is seen. Based on this, we believe that the efficacy and safety data outlined in Section 2 is sufficient to support the use of Gleevec in these rare diseases.

   Do you agree with this strategy?

   FDA Response: Yes but with the reservation expressed in question 1.

3. Efficacy data to support the registration of Gleevec for these indications will be provided as outlined in Sections 2 and 4. The criteria to be used to evaluate response and/or meaningful therapeutic benefit over existing treatment for these serious or life-threatening illnesses will be defined in terms of either standard clinical criteria

(e.g. accepted criteria for response rates) or in some instances, overall clinical benefit will be described in comparison with historical data.

Is this acceptable?

FDA Response: This is a review issue. Overall clinical benefit will have to be acceptably defined.

4. The recommended starting dose for dermatofibrosarcoma protuberans (DFSP) will be 800 mg taken daily. For all other indications it will be —— mg taken daily, and may be increased based on the data and the physician's assessment. b(4)

   Is this acceptable?

   FDA Response: The proposed doses, if supported by efficacy data, are acceptable.

5. Novartis plans to provide best descriptive data that is feasible in support of the safety and efficacy of Gleevec in a number of selected, rare indications. It is unlikely that any meaningful statistical evaluations and testing can be performed with the limited data from this clinical trial (Novartis study B2225) and a small number of published case reports.

   Is this acceptable?

   FDA Response: Yes

6. No formal comparison with historical data on efficacy of other therapies will be made for these indications, other than descriptive comparisons when available data exists.

   Is this acceptable?

   FDA Response: Yes

7. There are sufficient data to support the rarity of these diseases in adult patients. The diseases are even more rare in pediatric patients. Novartis intends to seek a waiver from pediatric labeling requirements due to the very rare occurrence in children in these diseases.

   Do you agree?

   FDA Response: We think the question of pediatric studies should be further explored.

Clinical Pharmacology Comment:

You plan to correlate the dose and pharmacokinetic (PK) parameters, as well as the changes in imaging/molecules with clinical outcomes in this proposed clinical study. If feasible, we recommend that you also correlate the PK of Gleevec and the effects on imaging/molecules markers change with the clinical efficacy/safety endpoints.

FINAL PROTOCOLS

Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF) should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs till 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by will be made available to the public on the Internet at http://clinicaltrials.gov.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

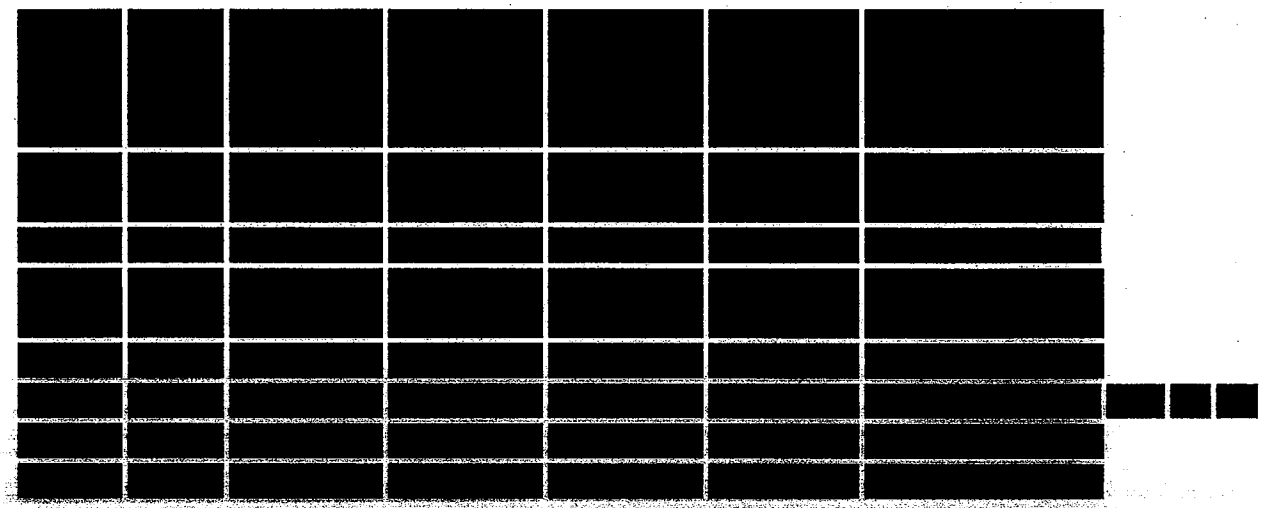
PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.



CHEMISTRY

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-588	Efficacy Supplement Type SE-1	Supplement Number 011, 012, 013, 014, 017	
Drug: Gleevec (imatinib)		Applicant:	
RPM: Staten (Pease)		HFD-150	Phone # 61434

Application Type: (X) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard () Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	orphan
❖ User Fee Goal Dates	10-19-06; 10-21-06; 1-1-07; 1-29-07
❖ Special programs (indicate all that apply)	(X) None Subpart H () 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (**X**) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(**X**) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(**X**) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) (**X**) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(**X**) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (**X**) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	S011 and S012 3-14-06 S013 [redacted] 3-15-06 S014 and S017 6-7-06

b(4)

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (X) ~~Talk Paper~~ Burst ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Attached to letter
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	6-7-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	9-6-06 e-mail
• Documentation of discussions and/or agreements relating to post-marketing commitments	Novartis' 9-25-06 response
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	8-12-04
• Pre-NDA meeting (indicate date)	1-10-05
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9-9-06 joint (S011) 9-14-06 joint (S012) 9-9-06 joint (S013) 9-14-06 joint (S014) 9-14-06 joint (S017)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Not required (see tab)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	Page 36 (S011) in review Page 45 (S012) in review Page 41 (S013) in review Page 39 (S014) in review Page 46 (S017) in review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	n/a all orphan indications
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	Joint reviews – see above
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9-21-06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	n/a
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	S011, S012 3-15-06 S013 — 3-23-06 S014 5-12-06 S017 6-28-06 b(4)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See reviews above
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: n/a ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	n/a
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).