NOVARTIS

T2006-XX

Gleevec®

(imatinib mesylate)

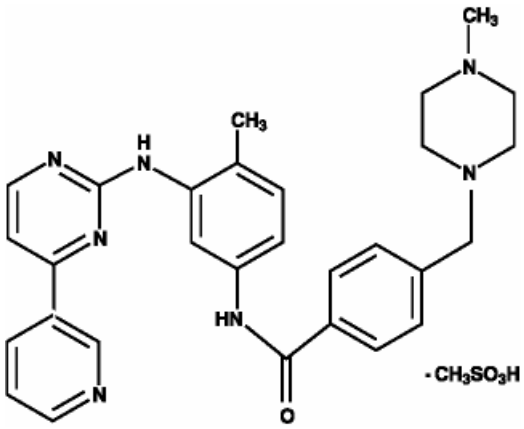
Tablets

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 ≤ 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

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

Figure 1 Time to Progression (ITT)

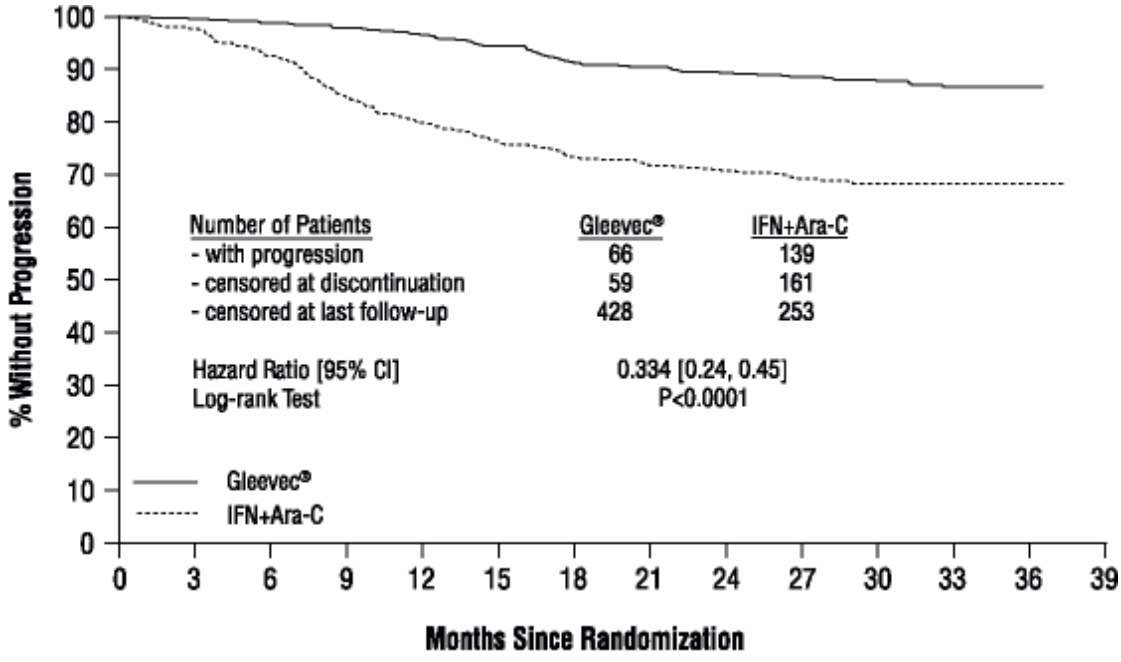
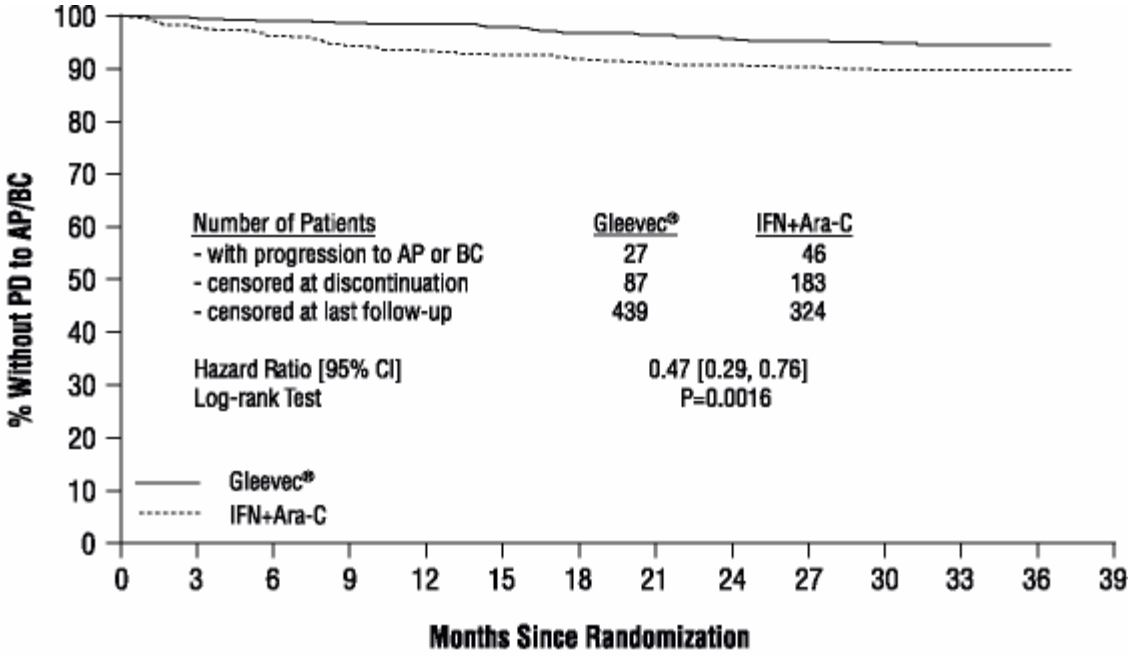


Figure 2 Time to Progression to AP or BC (ITT)



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.

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

Hematologic Toxicity

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

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

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

Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 12) 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.

Adverse Reactions in Pediatric Population

The overall safety profile of pediatric patients treated with Gleevec in 93 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. Nausea and vomiting were the most commonly reported individual AEs with an incidence similar to that seen in adult patients. Although most patients experienced AEs at some time during the study, the incidence of Grade 3/4 AEs was low.

Adverse Effects in Other Subpopulations

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

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 eosinophilic 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.

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