NOVARTIS

T200-

# Gleevec®
## (imatinib mesylate)

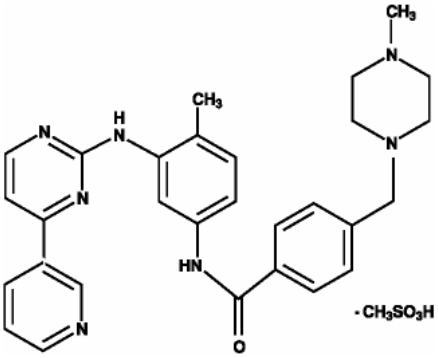
**Tablets**

**Rx only**

**Prescribing Information**

## DESCRIPTION

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




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

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

# CLINICAL PHARMACOLOGY

## Mechanism of Action

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

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

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

## Pharmacokinetics

The pharmacokinetics of Gleevec® (imatinib mesylate) have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with $C_{max}$ achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and $\alpha_1$-acid glycoprotein.

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

## Metabolism and Elimination

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

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

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

## Special Populations

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

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

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

## Drug-Drug Interactions

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

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

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

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

# CLINICAL STUDIES

## Chronic Myeloid Leukemia

### *Chronic Phase, Newly Diagnosed*

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

A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 14 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec were still receiving first-line treatment. Due to discontinuations and cross-overs, only 30% of patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of consent (13.4%) 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 (22.8%).

The primary efficacy endpoint of the study was progression-free survival (PFS). The final analysis of progression-free survival was planned after 5 years, however, the reported analysis was conducted at one year after the last patient was randomized to the study. 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. A total of 218 patients crossed over from the interferon arm to the Gleevec arm, and 7 patients crossed over from the Gleevec arm to the interferon arm. The estimated rate of progression-free survival at 12 months in the ITT population was 97.2% in the Gleevec arm and 80.3% in the control arm. (Figure 1.) The estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 12 months was 98.5% in the Gleevec arm compared to the 93.1% in the IFN arm. (Figure 2.) There were 11 and 20 deaths reported in the Gleevec and IFN arm, respectively.

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

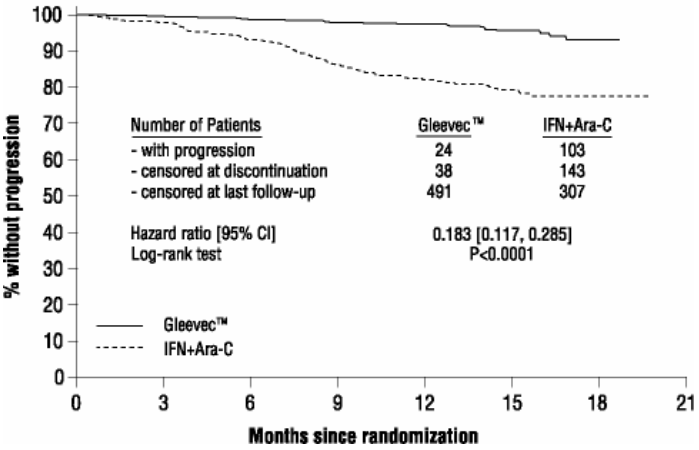
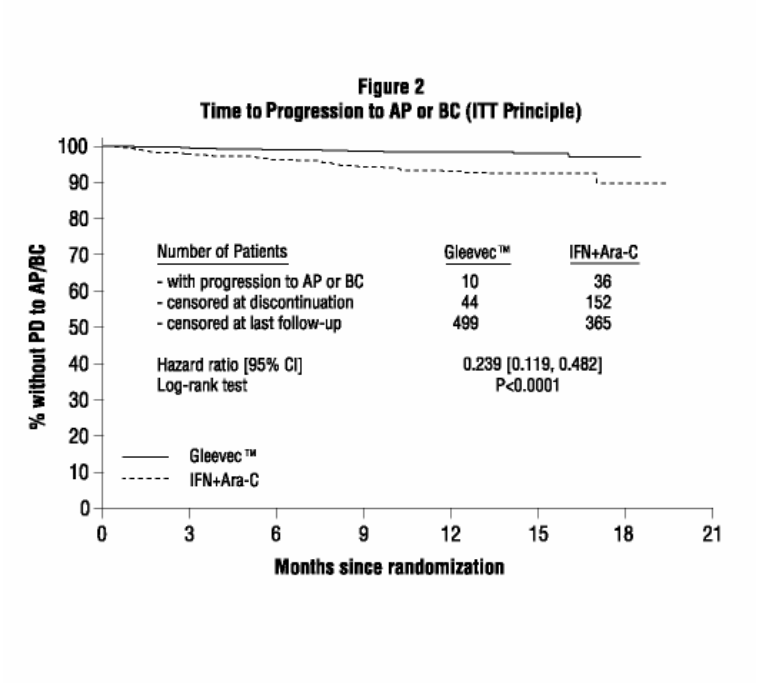



**Figure 2**
**Time to Progression to AP or BC (ITT Principle)**




Major cytogenetic response, hematologic response, time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 1. 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 1 Response in Newly Diagnosed CML Study (First-Line)**

| (Best Response Rates) | Gleevec® n=553 | IFN+Ara-C n=553 |
|---|---|---|
| **Hematologic Response**[1] | | |
| CHR Rate n (%) | 522 (94.4%)* | 302 (54.6%)* |
| [95% CI] | [92.1%, 96.2%] | [50.4%, 58.8%] |
| **Cytogenetic Response**[2] | | |
| **Major Cytogenetic Response n (%)** | 419 (75.8%)* | 67 (12.1%)* |
| [95% CI] | [72.0%, 79.3%] | [9.5%, 15.1%] |
| Unconfirmed[3] | 82.6%* | 20.3%* |
| **Complete Cytogenetic Response n (%)** | 297 (53.7%)* | 15 (2.7%)* |
| Unconfirmed[3] | 67.8%* | 7.4%* |

* 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.

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

### *Late Chronic Phase CML and Advanced Stage CML*

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

### Chronic Phase, Prior Interferon-Treatment

532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon: failure to achieve (within 6 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥25 x $10^6$ IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+

metaphases). Median duration of treatment was 29 months with 81% of patients treated for ≥24 months (maximum = 31.5 months). Efficacy results are reported in Table 2. Confirmed major cytogenetic response rates were higher in patients with IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

## Accelerated Phase

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

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

## Myeloid Blast Crisis

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

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

**Table 2 Response in CML Studies**

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

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

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

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

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

BM=bone marrow, PB=peripheral blood

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

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

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

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

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

## Pediatric CML

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

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

## Gastrointestinal Stromal Tumors

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

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

**Table 3 Tumor Response in GIST Study**

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

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

## INDICATIONS AND USAGE

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

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

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

## CONTRAINDICATIONS

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

## WARNINGS

### Pregnancy

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

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

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

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

# PRECAUTIONS

## General

***Dermatologic Toxicities:*** Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec. 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® (imatinib mesylate) 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 0.9% 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 2%-6% of other adult CML patients taking Gleevec [10]. There have been post-marketing reports, including fatalities, of cerebral edema, increased intracranial pressure, and papilledema in patients with CML treated with Gleevec.

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

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

***Hemorrhage:*** In the newly diagnosed CML trial, 0.7% of patients had grade 3/4 hemorrhage. In the GIST clinical trial seven patients (5%), four in the 600-mg dose group and three in the 400-mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

***Hematologic Toxicity:*** Treatment with Gleevec is associated with anemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

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

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

## Drug Interactions

### *Drugs that may alter imatinib plasma concentrations*

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

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

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

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

### *Drugs that may have their plasma concentration altered by Gleevec*

Gleevec increases the mean $C_{max}$ and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma

concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

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

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

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

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

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

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

## Pregnancy

### *Pregnancy Category D. (See WARNINGS.)*

## Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking Gleevec.

## Pediatric Use

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

## Geriatric Use

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

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

# ADVERSE REACTIONS

## Chronic Myeloid Leukemia

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

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

A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These events were usually managed by interrupting Gleevec treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life 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 4 and 5.

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

| | All Grades | | CTC Grades 3/4 | |
|---|---|---|---|---|
| | Gleevec® | IFN+Ara-C | Gleevec™ | IFN+Ara-C |

| Preferred Term | N=551 (%) | N=533 (%) | N=551 (%) | N=533 (%) |
|---|---|---|---|---|
| Fluid Retention | 54.1 | 10.1 | 0.9 | 0.9 |
| - Superficial Edema | 53.2 | 8.8 | 0.9 | 0.4 |
| - Other Fluid Retention Events | 3.4 | 1.5 | 0 | 0.6 |
| Nausea | 42.5 | 60.8 | 0.4 | 5.1 |
| Muscle Cramps | 35.4 | 9.9 | 1.1 | 0.2 |
| Musculoskeletal Pain | 33.6 | 40.5 | 2.7 | 7.7 |
| Rash | 31.9 | 25.0 | 2.0 | 2.1 |
| Fatigue | 30.7 | 64.7 | 1.1 | 24.0 |
| Diarrhea | 30.3 | 40.9 | 1.3 | 3.2 |
| Headache | 28.5 | 41.8 | 0.4 | 3.2 |
| Joint Pain | 26.7 | 38.3 | 2.2 | 6.8 |
| Abdominal Pain | 23.4 | 22.9 | 2.0 | 3.6 |
| Myalgia | 20.9 | 38.6 | 1.5 | 8.1 |
| Nasopharyngitis | 19.2 | 7.7 | 0 | 0.2 |
| Hemorrhage | 18.9 | 19.9 | 0.7 | 1.3 |
| Dyspepsia | 15.1 | 9.0 | 0 | 0.8 |
| Vomiting | 14.7 | 26.6 | 0.9 | 3.4 |
| Pharyngolaryngeal Pain | 14.2 | 11.4 | 0.2 | 0 |
| Dizziness | 13.2 | 23.1 | 0.5 | 3.4 |
| Cough | 12.5 | 21.6 | 0.2 | 0.6 |
| Upper Respiratory Tract Infection | 12.5 | 7.9 | 0.2 | 0.4 |
| Pyrexia | 11.8 | 38.6 | 0.5 | 2.8 |
| Weight Increased | 11.6 | 1.5 | 0.7 | 0.2 |
| Insomnia | 11.4 | 18.4 | 0 | 2.3 |

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

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

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

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

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

## Hematologic Toxicity

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

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

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

## Hepatotoxicity

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

## Adverse Reactions in Pediatric Population

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

## Adverse Effects in Other Subpopulations

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

**Table 6 Lab Abnormalities in Newly Diagnosed CML Trial**

| | Gleevec® N=551 % | | IFN+Ara-C N=533 % | |
|---|---|---|---|---|
| **CTC Grades** | **Grade 3** | **Grade 4** | **Grade 3** | **Grade 4** |
| **Hematology Parameters** | | | | |
| - Neutropenia* | 11.4 | 2.2 | 20.3 | 4.3 |
| - Thrombocytopenia* | 6.9 | 0.2 | 15.8 | 0.6 |
| - Anemia | 2.7 | 0.4 | 4.1 | 0.2 |
| **Biochemistry Parameters** | | | | |
| - Elevated Creatinine | 0 | 0 | 0.4 | 0 |
| - Elevated Bilirubin | 0.2 | 0.5 | 0.2 | 0 |
| - Elevated Alkaline Phosphatase | 0.2 | 0 | 0.8 | 0 |
| - Elevated SGOT (AST) | 2.9 | 0.2 | 3.8 | 0.4 |
| - Elevated SGPT (ALT) | 3.1 | 0.4 | 5.6 | 0 |

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

**Table 7 Lab Abnormalities in Other CML Clinical Trials**

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

CTC grades: neutropenia (grade 3 ≥0.5-1.0 x $10^9$/L), grade 4 <0.5 x $10^9$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)

## Gastrointestinal Stromal Tumors

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

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

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

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

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

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

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 9.

**Table 9 Laboratory Abnormalities in GIST Trial**

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

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

## Additional Data From Multiple Clinical Trials

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

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

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

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

**Digestive**: *Less common*: abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent*: gastric ulcer, gastroenteritis, gastritis *Rare*: colitis, ileus/intestinal obstruction, pancreatitis

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

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

**Hypersensitivity**: *Rare*: angioedema

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

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

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

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

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

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

**Respiratory:** *Rare*: interstitial pneumonitis, pulmonary fibrosis

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

**Vascular Disorders:** *Rare*: thrombosis/embolism

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## OVERDOSAGE

Experience with doses greater than 800 mg is limited. In the event of overdosage, the patient should be observed and appropriate supportive treatment given. An oral dose of 1200 mg/m$^2$/day, approximately 2.5 times the human dose of 800 mg, based on body surface area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m$^2$/day, approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10 administrations, due to general deterioration of the animals with secondary degenerative histological changes in many tissues.

## DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

## Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse Reactions

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

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

## Dose Adjustment for Hematologic Adverse Reactions

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

Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia

| | | |
|---|---|---|
| Chronic Phase CML (starting dose 400mg[1]) or GIST (starting dose either 400 mg or 600 mg) | ANC <1.0 x $10^9$/L and/or Platelets <50 x $10^9$/L | 1. Stop Gleevec until ANC ≥1.5 x $10^9$/L and platelets ≥75 x $10^9$/L<br>2. Resume treatment with Gleevec at the original starting dose of 400 mg[1] or 600 mg<br>3. If recurrence of ANC <1.0 x $10^9$/L and/or platelets <50 x $10^9$/L, repeat step 1 and resume Gleevec at a reduced dose (300 mg[2] if starting dose was 400 mg[1], 400 mg if starting dose was 600 mg) |
| Accelerated Phase CML and Blast Crisis (starting dose 600 mg) | [3]ANC <0.5 x $10^9$/L and/or Platelets <10 x $10^9$/L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)<br>2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg<br>3. If cytopenia persist 2 weeks, reduce further to 300 mg<br>4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x $10^9$/L and platelets ≥20 x $10^9$/L and then resume treatment at 300 mg. |

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

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

[3]occurring after at least 1 month of treatment

# HOW SUPPLIED

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

## 100 mg Tablets

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

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

## 400 mg Tablets

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

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

## Storage

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

Dispense in a tight container, USP.

T200

REV: Printed in U.S.A.

NOVARTIS

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