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Gleevec™
(imatinib mesylate)

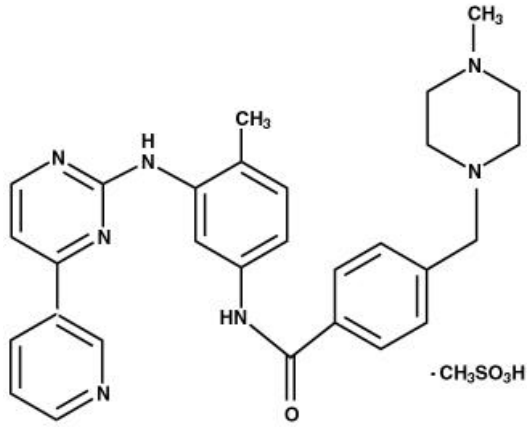
Capsules

Rx only

Prescribing Information

DESCRIPTION

Gleevec™ capsules contain imatinib mesylate equivalent to 100 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 relative molecular mass is 589.7. Imatinib mesylate is very soluble in water and 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), magnesium stearate (NF) and microcrystalline cellulose (NF). Capsule shell: gelatin, iron oxide, red (E172); iron oxide, yellow (E172); titanium dioxide (E171).

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 500 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule formulation is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25 mg-1000 mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein.

The pharmacokinetics of imatinib were 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-labelled 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: There are no pharmacokinetic data in pediatric patients.

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

CYP3A4 Inducers: No formal study of CYP3A4 inducers has been conducted, but a patient on chronic therapy with phenytoin (a CYP3A4 inducer) given 350 mg daily dose of Gleevec had an AUC_{0-24} about one fifth of the typical AUC_{0-24} of 20 μg•h/mL. This probably reflects the induction of CYP3A4 by phenytoin. (See PRECAUTIONS.)

In vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 μM, respectively. Imatinib 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

Three international, open-label, single-arm studies were conducted in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML): 1) in the chronic phase after failure of interferon-alfa (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 $x10^6$ 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). Efficacy results are reported in Table 1. Results were similar in the three subgroups described above.

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; <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. Efficacy results are reported in Table 1. Response rates in accelerated phase CML were higher for the 600 mg dose group than for the 400 mg group: hematologic response (73% vs. 62%), confirmed and unconfirmed major cytogenetic response (28% vs. 18%).

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. Efficacy results are reported in Table 1. 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 1 Response in CML Patients in Clinical 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]	**93% [91.0-95.4]**	**69% [63.0-75.2]**	**31% [25.2-36.8]**
Complete hematologic response (CHR)	93%	37%	7%
No evidence of leukemia (NEL)	Not applicable	12%	5%
Return to chronic phase (RTC)	Not applicable	20%	19%
Major Cytogenetic Response[2] (unconfirmed[3])	**53% [48.7-57.3]** (61%)	**19% [14.3-24.8]** (25%)	**7% [4.2-10.7]** (15%)
Complete[4] (unconfirmed[3])	32% (41%)	13% (17%)	1.5% (7%)

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

CHR: Chronic phase study [WBC <10 $x10^9$/L, platelet <450 $x10^9$/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 $x10^9$/L, platelets 100 $x10^9$/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: same criteria as for CHR but ANC 1 $x10^9$/L and platelets 20 $x10^9$/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]Major Cytogenetic Response: A major response combines both complete and partial responses: complete (0% Ph^+ metaphases), partial (1%-35% Ph^+ metaphases).

[3]Unconfirmed cytogenetic response is basd on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogentic 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. Response duration cannot be precisely defined because follow-up on most patients is relatively short. In blast crisis, the estimated median duration of hematologic response is about 10 months. In accelerated phase, median duration of hematologic response is greater than 12 months but cannot yet be estimated. Follow-up is insufficient to estimate duration of cytogenetic response in all studies.

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.

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-4052, 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 2.

Table 2 Tumor responses in trial GIST

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 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 patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors)

The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and objective response rate in GIST (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 this dose also experienced significant post-implantation loss in the form of early fetal resorption. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. These effects were not seen at doses 30 mg/kg (one-third the maximum human dose of 800 mg).

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

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 imatinib dose and age >65 years in the CML studies. Severe fluid retention (e.g. pleural effusion, pericardial effusion, pulmonary edema, and ascites) was reported in 2% to 8% of patients taking Gleevec for CML. In addition, severe superficial edema was reported in 2% to 5% of the patients with CML.

Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1% to 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 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 (3patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

Hematologic Toxicity: Treatment with Gleevec is associated with neutropenia or 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: Because follow-up of most patients treated with imatinib is relatively short , there are no long-term safety data on Gleevec treatment. 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 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 co-administered 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, rifampicin, phenobarbital or St. John's Wort) may reduce exposure to Gleevec. No formal study of CYP3A4 inducers has been conducted, but a patient on chronic therapy with phenytoin (a CYP3A4 inducer) given 350 mg daily dose of Gleevec had an AUC_{0-24} about one fifth of the typical AUC_{0-24} of 20 µg•h/mL. This probably reflects the induction of CYP3A4 by phenytoin. (See PRECAUTIONS.)

Drugs that may have their plasma concentration altered by Gleevec

Imatinib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5- fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib. 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 co-administered 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 equal to 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. At a dose of 60 mg/kg (approximately equal to the human dose of 800 mg), female rats had significant post-implantation fetal loss and a reduced number of live fetuses. This was not seen at doses 20 mg/kg (one-fourth the maximum human dose of 800 mg).

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/or its metabolites were extensively excreted in milk. 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

The safety and effectiveness of Gleevec in pediatric patients have not been established.

Geriatric Use

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. 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 adverse events in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were nausea, vomiting, diarrhea, edema, and muscle cramps (Table 3). 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 2%-5%. 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 Table 3.

Table 3 Adverse Experiences Reported in CML Clinical Trials (³ 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**
Nausea	70	4	71	5	60	2
Fluid retention	71	12	73	6	66	3
– Superficial edemas	67	5	71	4	64	2
– Other fluid retention events[2]	22	8	10	3	7	2
Muscle cramps	27	0.8	42	0.4	55	1
Diarrhea	42	4	55	4	43	2
Vomiting	54	4	56	3	32	1
Hemorrhage	52	19	44	9	22	2
– CNS hemorrhage	7	5	2	0.9	1	1
– Gastrointestinal hemorrhage	8	3	5	3	2	0.4
Musculoskeletal pain	43	9	46	9	35	2
Skin rash	35	5	44	4	42	3
Headache	27	5	30	2	34	0.2
Fatigue	29	3	41	4	40	1
Arthralgia	25	4	31	6	36	1
Dyspepsia	11	0	21	0	24	0
Myalgia	8	0	22	2	25	0.2
Weight increased	5	0.8	14	3	30	5
Pyrexia	41	7	39	8	17	1
Abdominal pain	31	6	33	3	29	0.6
Cough	14	0.8	26	0.9	17	0
Dyspnea	14	4	20	7	9	0.6
Anorexia	14	2	17	2	6	0
Constipation	15	2	15	0.9	6	0.2
Nasopharingitis	8	0	16	0	18	0.2
Night sweats	12	0.8	14	1	10	0.2
Pruritus	8	1	13	0.9	12	0.8
Epistaxis	13	3	13	0	5	0.2
Hypokalemia	13	4	8	2	5	0.2
Petechiae	10	2	5	0.9	1	0
Pneumonia	12	6	8	6	3	0.8
Weakness	12	3	9	3	7	0.2
Upper respiratory tract infection	3	0	9	0.4	15	0
Dizziness	11	0.4	12	0	13	0.2
Insomnia	10	0	13	0	13	0.2
Sore throat	8	0	11	0	11	0
Ecchymosis	11	0.4	6	0.9	2	0
Rigors	10	0	11	0.4	8	0
Asthenia	5	2	11	2	6	0
Influenza	0.8	0.4	6	0	10	0.2

[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 I study). The occurrence of cytopenias in CML patients was also dependent on the stage of the disease, with a frequency of grade 3 or 4 neutropenia and thrombocytopenia between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase (see Table 4). The median duration of the neutropenic and thrombocytopenic episodes ranged usually from 2 to 3 weeks, and from 3 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 1% - 4% (see Table 4) 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 0.5% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

Adverse Effects in Subpopulations

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 older patients (65 years old). With the exception of a slight increase in the frequency of grade 1/2 periorbital edema, headache and fatigue in women, there was no evidence of a difference in the incidence or severity of adverse events between the sexes. No differences were seen related to race but the subsets were too small for proper evaluation.

TABLE 4 – Lab abnormalities in CML Clinical Trials

	Myeloid blast crisis (n= 260) 600 mg n=223 400mg n=37 (%)		Accelerated phase (n=235) 600 mg n=158 400mg n=77 (%)		Chronic phase, IFN failure n=532 400 mg (%)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology parameters						
• Neutropenia	16	48	23	36	27	8
• Thrombocytopenia	29	33	31	13	19	<1
• Anemia	41	11	34	6	6	1
Biochemistry parameters						
• Elevated creatinine	1.5	0	1.3	0	0.2	0
• Elevated bilirubin	3.8	0	2.1	0	0.8	0
• Elevated alkaline phosphatase	4.6	0	5.1	0.4	0.2	0
• Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
• Elevated SGPT (ALT)	2.3	0.4	3.8	0	1.9	0

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

Gastrointestinal Stromal Tumors

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

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec are shown in Table 5. 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 5 Adverse Experiences Reported in GIST trial (10% of all patients at either dose)[1]

	All CTC Grades		CTC Grade 3/4	
Initial dose (mg/day)	**400 mg**	**600 mg**	**400 mg**	**600 mg**
	(n=73)	**(n=74)**	**(n=73)**	**(n=74)**
Preferred Term	**%**	**%**	**%**	**%**
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
G-I 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

[2] Other fluid retention events included pleural effusion and ascites

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 6.

Table 6 Laboratory abnormalities in GIST trial

Parameter	400 mg (n=73) (%)		600 mg (n=74) (%)	
CTC Grade	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)

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 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.

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

The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for patients with unresectable and/or metastatic, malignant GIST.

In CML, dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in 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; loss of a previously achieved hematologic response.

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. 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).

Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 7.

Table 7 Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML or GIST (starting dose 400 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 dose of 400 mg 3. If 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 300 mg
Accelerated Phase CML and Blast Crisis or GIST (starting dose 600 mg)	[1]ANC <0.5 x10^9/L and/or Platelets <10 x10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persist 2 weeks, reduce further to 300 mg 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC 1 x10^9/L and platelets 20 x10^9/L and then resume treatment at 300 mg

[1]occurring after at least 1 month of treatment

Pediatric

The safety and efficacy of Gleevec in patients under the age of 18 years have not been established.

HOW SUPPLIED

Each hard gelatin capsule contains 100 mg of imatinib free base.

100 mg Capsules

Orange to grayish orange opaque capsule with “NVR SI” printed in red ink.
Bottles of 120 capsules .....NDC 0078-0373-66

Storage

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

Dispense in a tight container, USP.

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NOVARTIS

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