

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gleevec safely and effectively. See full prescribing information for Gleevec.

GLEEVEC (imatinib mesylate) tablets for oral use

Initial U.S. Approval: 2001

RECENT MAJOR CHANGES

Indications and Usage Ph+ CML - Pediatrics (1.3), Ph+ ALL (1.4), MDS/MPD (1.5), ASM (1.6), HES/CEL (1.7), DFSP (1.8), 11/2006

Dosage and Administration Ph+ CML - Pediatrics (2.2), Ph+ ALL (2.3), MDS/MPD (2.4), ASM (2.5), HES/CEL (2.6), DFSP (2.7) 11/2006

Warnings and Precautions Severe Congestive Heart Failure and Left Ventricular Dysfunction (5.4) 11/2006

INDICATIONS AND USAGE

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Follow-up is limited to 5 years (1.1).
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2).
- Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival (1.3).
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.4).
- Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements (1.5).
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown (1.6).
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR α fusion kinase negative or unknown (1.7).
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). The effectiveness of Gleevec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. (1.9).

DOSAGE AND ADMINISTRATION

- Adults with Ph+ CML CP (2.1): 400 mg/day
- Adults with Ph+ CML AP or BC (2.1): 600 mg/day
- Pediatrics with Ph+ CML (2.2): 340 mg/m²/day or 260 mg/m²/day
- Adults with Ph+ ALL (2.3): 600 mg/day
- Adults with MDS/MPD (2.4): 400 mg/day
- Adults with ASM (2.5): 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.6): 100 mg/day or 400 mg/day
- Adults with DFSP (2.7): 800 mg/day
- Adults with GIST (2.8): 400 mg/day or 600 mg/day
- Patients with mild to moderate hepatic impairment (2.9): 400 mg/day
- Patients with severe hepatic impairment (2.9): 300 mg/day

All doses of Gleevec should be taken 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. Gleevec can

be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

DOSAGE FORMS AND STRENGTHS

Tablets (scored): 100 mg and 400 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.1, 8.1)
- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics. (5.2, 6.1)
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter. (5.3)
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated. (5.4)
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. (5.5)
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST. (5.6)
- Gastrointestinal perforations, some fatal, have been reported. (5.7)
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Gleevec in patients with conditions associated with high eosinophil levels (e.g. HES, MDS/MPD and ASM). (5.8)
- Bullous dermatologic reactions (e.g. erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Gleevec. (5.9)
- Consider potential toxicities, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use. (5.10)

ADVERSE REACTIONS

The most frequently reported adverse reactions ($\geq 10\%$) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain (6.1, 6.11)

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1-888-NOW-NOVA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inducers may decrease Gleevec C_{max} and AUC (2.9, 7.1)
- CYP3A4 inhibitors may increase Gleevec C_{max} and AUC (7.2)
- Gleevec is an inhibitor of CYP3A4 and may increase the C_{max} and AUC of other drugs (7.3)
- Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin (7.3)
- Systemic exposure to acetaminophen is expected to increase when co-administered with Gleevec (7.5)

USE IN SPECIFIC POPULATIONS

- There is no experience in children less than 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. Follow-up is limited to 5 years.

1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy

Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

1.3 Pediatric Patients with Ph+ CML in Chronic Phase

Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

1.4 Ph+ Acute Lymphoblastic Leukemia (ALL)

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia

1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

Adult patients with myelodysplastic/ myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements

1.6 Aggressive Systemic Mastocytosis (ASM)

Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown

1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR α fusion kinase negative or unknown

1.8 Dermatofibrosarcoma Protuberans (DFSP)

Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans

1.9 Kit+ Gastrointestinal Stromal Tumors (GIST).

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. The effectiveness of Gleevec in GIST is based on objective response rate [see *Clinical Studies* (14.8)]. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

2 DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Gleevec treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 2 years of age.

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).

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

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

2.1 Adult Patients with Ph+ CML CP, AP and BC

The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

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.

2.2 Pediatric Patients with Ph+ CML

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). The recommended Gleevec dose is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

2.3 Ph+ ALL

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

2.4 MDS/MPD

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

2.5 ASM

The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR α , a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

2.6 HES/CEL

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

2.7 DFSP

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

2.8 GIST

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

2.9 Dose Modification Guidelines

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored. [see *Drug Interactions (7.1)*]

Hepatic Impairment: Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. [See *Use in Specific Populations (8.6)*]

2.10 Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m²/day to 260 mg/m²/day or from 260 mg/m²/day to 200 mg/m²/day, respectively.

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.

2.11 Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

ASM associated with eosinophilia (starting dose 100 mg)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none">1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.2. Resume treatment with Gleevec at previous dose (i.e. dose before severe adverse reaction).
HES/CEL with FIP1L1-PDGFR α fusion kinase (starting dose 100 mg)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none">1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.2. Resume treatment with Gleevec at previous dose (i.e. dose before severe adverse reaction).
Chronic Phase CML (starting dose 400 mg)	ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$	<ol style="list-style-type: none">1. Stop Gleevec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.2. Resume treatment with Gleevec at the original starting dose of 400 mg or 600 mg
MDS/MPD, ASM and HES/CEL (starting dose 400 mg)		<ol style="list-style-type: none">3. If recurrence of ANC $< 1.0 \times 10^9/L$ and/or platelets $< 50 \times 10^9/L$, repeat step 1 and resume Gleevec at a reduced dose (300 mg if starting dose was 400 mg, 400 mg if starting dose was 600 mg)
GIST (starting dose either 400 mg or 600 mg)		
Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg)	ANC $< 0.5 \times 10^9/L$ and/or platelets $< 10 \times 10^9/L$	<ol style="list-style-type: none">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
Ph+ ALL (starting dose 600 mg)		<ol style="list-style-type: none">3. If cytopenia persists 2 weeks, reduce further to 300 mg4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC $\geq 1 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$ and then resume treatment at 300 mg

DFSP (starting dose 800 mg)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50 x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC ≥ 1.5 x10⁹/L and platelets ≥ 75 x10⁹/L. 2. Resume treatment with Gleevec at 600 mg 3. In the event of recurrence of ANC < 1.0 x10⁹/L and/or platelets < 50 x10⁹/L, repeat step 1 and resume Gleevec at reduced dose of 400 mg.
Pediatric newly diagnosed chronic phase CML (starting dose 340 mg/m ²)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50 x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC ≥ 1.5 x10⁹/L and platelets ≥ 75 x10⁹/L. 2. Resume treatment with Gleevec at previous dose (i.e. dose before severe adverse reaction) 3. In the event of recurrence of ANC < 1.0 x10⁹/L and/or platelets < 50 x10⁹/L, repeat step 1 and resume Gleevec at reduced dose of 260 mg/m²
Pediatric patients with chronic phase CML recurring after transplant or resistant to Interferon (starting dose 260 mg/m ²)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50 x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Gleevec until ANC ≥ 1.5 x10⁹/L and platelets ≥ 75 x10⁹/L. 2. Resume treatment with Gleevec at previous dose (i.e. dose before severe adverse reaction) 3. In the event of recurrence of ANC < 1.0 x10⁹/L and/or platelets < 50 x10⁹/L, repeat step 1 and resume Gleevec at reduced dose of 200 mg/m²

3 DOSAGE FORMS AND STRENGTHS

100 mg film coated 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

400 mg film coated tablets

Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “400” on one side with score on the other side, and “SL” on each side of the score

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

Pregnancy Category D

Women of childbearing potential should be advised to avoid becoming pregnant while taking Gleevec. Sexually active female patients taking Gleevec should use adequate contraception.

Gleevec can cause fetal harm when administered to a pregnant woman. 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).

There are no adequate and well-controlled studies with Gleevec in pregnant women. Women should be advised not to become pregnant when taking Gleevec. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5.2 Fluid Retention and Edema

Gleevec is often associated with edema and occasionally serious fluid retention [see *Adverse Reactions (6.1)*]. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.5% 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) reactions were reported in 1.3% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

5.3 Hematologic Toxicity

Treatment with Gleevec is associated with anemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In pediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy. [See *Dosage and Administration (2.11)*].

5.4 Severe Congestive Heart Failure and Left Ventricular Dysfunction

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

5.5 Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Gleevec [see *Adverse Reactions (6.3)*]. 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 (2.10)*]

5.6 Hemorrhage

In the newly diagnosed CML trial, 1.8% 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 reactions 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.

5.7 Gastrointestinal Disorders

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

5.8 Hypereosinophilic Cardiac Toxicity

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

5.9 Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Gleevec.

5.10 Toxicities From Long-Term Use

It is important to consider potential toxicities suggested by animal studies, specifically, *liver, kidney and cardiac 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). Additional long-term toxicities were identified in a 2-year rat study. Histopathological examination of the treated rats that died on study revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Non-neoplastic lesions seen in this 2-year study which were not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

6.1 Chronic Myeloid Leukemia

The majority of Gleevec-treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade, but drug was discontinued for drug-related adverse reactions in 2.4% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon-alpha therapy, 4% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse reactions were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 2 for newly diagnosed CML, Table 3 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. [see *Dosage and Administration (2.10)*] The frequency of severe superficial edema was 1.5%-6%.

A variety of adverse reactions represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These reactions 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 reactions were usually managed by interrupting Gleevec treatment and using diuretics or other appropriate supportive care measures. A few of these reactions may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the Gleevec treated patients are shown in Tables 2 and 3.

Table 2 Adverse Reactions Reported in Newly Diagnosed CML Clinical Trial (≥10% of Gleevec treated patients) ⁽¹⁾

All Grades

CTC Grades 3/4

Preferred Term	Gleevec	IFN+Ara-C	Gleevec	IFN+Ara-C
	N=551 (%)	N=533 (%)	N=551 (%)	N=533 (%)
Fluid Retention	61.7	11.1	2.5	0.9
- Superficial Edema	59.9	9.6	1.5	0.4
- Other Fluid Retention Reactions ²	6.9	1.9	1.3	0.6
Nausea	49.5	61.5	1.3	5.1
Muscle Cramps	49.2	11.8	2.2	0.2
Musculoskeletal Pain	47.0	44.8	5.4	8.6
Diarrhea	45.4	43.3	3.3	3.2
Rash and Related Terms	40.1	26.1	2.9	2.4
Fatigue	38.8	67.0	1.8	25.1
Headache	37.0	43.3	0.5	3.8
Joint Pain	31.4	38.1	2.5	7.7
Abdominal Pain	36.5	25.9	4.2	3.9
Nasopharyngitis	30.5	8.8	0	0.4
Hemorrhage	28.9	21.2	1.8	1.7
- GI Hemorrhage	1.6	1.1	0.5	0.2
- CNS Hemorrhage	0.2	0.4	0	0.4
Myalgia	24.1	38.8	1.5	8.3
Vomiting	22.5	27.8	2.0	3.4
Dyspepsia	18.9	8.3	0	0.8
Cough	20.0	23.1	0.2	0.6
Pharyngolaryngeal Pain	18.1	11.4	0.2	0
Upper Respiratory Tract Infection	21.2	8.4	0.2	0.4
Dizziness	19.4	24.4	0.9	3.8
Pyrexia	17.8	42.6	0.9	3.0
Weight Increased	15.6	2.6	2.0	0.4
Insomnia	14.7	18.6	0	2.3
Depression	14.9	35.8	0.5	13.1
Influenza	13.8	6.2	0.2	0.2
Bone pain	11.3	15.6	1.6	3.4
Constipation	11.4	14.4	0.7	0.2
Sinusitis	11.4	6.0	0.2	0.2

⁽¹⁾All adverse reactions occurring in $\geq 10\%$ of Gleevec treated patients are listed regardless of suspected relationship to treatment.

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

Table 3 Adverse Reactions Reported in Other CML Clinical Trials ($\geq 10\%$ of all patients in any trial)⁽¹⁾

Preferred Term	Myeloid Blast Crisis		Accelerated Phase		Chronic Phase, IFN Failure	
	(n=260)		(n=235)		(n=532)	
	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 reactions	22	6	15	4	7	2

(2)

Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Hemorrhage	53	19	49	11	30	2
- CNS Hemorrhage	9	7	3	3	2	1
- GI Hemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2
Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalemia	13	4	9	2	6	0.8
Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	0.4	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

⁽¹⁾ All adverse reactions occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship to treatment.

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

6.2 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). 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 4 and 5). 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 4 and 5). The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

These reactions 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.

Table 4 Lab Abnormalities in Newly Diagnosed CML Clinical Trial

CTC Grades	Gleevec N=551 %		IFN+Ara-C N=533 %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters*				
- Neutropenia*	13.1	3.6	20.8	4.5
- Thrombocytopenia*	8.5	0.4	15.9	0.6
- Anemia	3.3	1.1	4.1	0.2
Biochemistry Parameters				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.9	0.2	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated SGOT /SGPT	4.7	0.5	7.1	0.4

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

Table 5 Lab Abnormalities in Other CML Clinical Trials

CTC Grades ¹	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
	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

¹CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade 3 $\geq 10-50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (hemoglobin $\geq 65-80$ 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)

6.3 Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in approximately 5% of CML patients (see Table 4) and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1.0% of CML patients. One patient, who was taking acetaminophen regularly for fever, died of acute liver failure. In the GIST trial, grade 3 or 4 SGPT (ALT)

elevations were observed in 6.8% of patients and grade 3 or 4 SGOT (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in 2.7% of patients.

6.4 Adverse Reactions in Pediatric Population

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

6.5 Adverse Reactions 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 reactions. 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 that were related to race but the subsets were too small for proper evaluation.

6.6 Acute Lymphoblastic Leukemia

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

6.7 Myelodysplastic/Myeloproliferative Diseases

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec for MDS/MPD in the phase 2 study, are shown in Table 6.

Table 6 Adverse Reactions Reported (More than One Patient) in MPD Patients in the Phase 2 Study ($\geq 10\%$ All Patients) all Grades

Preferred Term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)
Muscle Cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital Edema	2 (28.6)

6.8 Aggressive Systemic Mastocytosis

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

6.9 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

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

6.10 Dermatofibrosarcoma Protuberans

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Gleevec for DFSP in the phase 2 study are shown in Table 7.

Table 7 Adverse Reactions Reported in DFSP Patients in the Phase 2 Study ($\geq 10\%$ All Patients) All Grades

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital Edema	4 (33.3)
Face Edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema Peripheral	4 (33.3)

Pyrexia	2 (16.7)
Eye Edema	4 (33.3)
Lacrimation Increased	3 (25.0)
Dyspnea Exertional	2 (16.7)
Anemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Gleevec for DFSP in the phase 2 study are presented in Table 8.

Table 8 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study

CTC Grades ¹	N=12	
	Grade 3	Grade 4
Hematology Parameters		
- Anemia	17 %	0 %
- Thrombocytopenia	17 %	0 %
- Neutropenia	0 %	8 %
Biochemistry Parameters		
- Elevated Creatinine	0 %	8 %

¹CTC Grades: neutropenia (Grade 3 ≥ 0.5 - $1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade 3 ≥ 10 - $50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), 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),

6.11 Gastrointestinal Stromal Tumors

The majority of Gleevec-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash. Most reactions were of mild-to-moderate severity. Drug was discontinued for adverse reactions in 7 patients (5%) in both dose levels studied. Superficial edema, most frequently periorbital or lower extremity edema, was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec. [see *Dosage and Administration (2.10)*] Severe (CTC Grade 3/4) superficial edema was observed in 3 patients (2%), including facial edema in one patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%).

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec are shown in Table 9. No major differences were seen in the severity of adverse reactions 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 9 Adverse Reactions Reported in GIST Trial ($\geq 10\%$ of all patients at either dose)⁽¹⁾

Preferred Term	All CTC Grades		CTC Grade 3/4	
	Initial dose (mg/day)		Initial dose (mg/day)	
	400 mg (n=73)	600 mg (n=74)	400 mg (n=73)	600 mg (n=74)
	%	%	%	%
Fluid Retention	81	80	7	12
- Superficial Edema	81	77	6	5
- Pleural Effusion or Ascites	15	12	3	8
Diarrhea	59	70	3	7
Nausea	63	74	6	4
Fatigue	48	53	1	1
Muscle Cramps	47	58	0	0
Abdominal Pain	40	37	11	4
Rash and Related Terms	38	53	4	3
Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1

Headache	33	39	0	0
Flatulence	30	34	0	0
Any Hemorrhage	26	34	6	11
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	4	4	4	3
- Other Hemorrhage(2)	22	27	0	5
Pyrexia	25	16	3	0
Back Pain	23	26	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper Respiratory Tract Infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0
Loose Stools	12	10	0	0
Operation	12	8	6	4
Pharyngolaryngeal Pain	12	7	0	0
Joint Pain	11	15	1	0
Constipation	11	10	0	1
Anxiety	11	7	0	0
Taste Disturbance	3	15	0	0

All adverse reactions occurring in $\geq 10\%$ of patients are listed regardless of suspected relationship to treatment.

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

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 10.

Table 10 Laboratory Abnormalities in GIST Trial

CTC Grades ¹	400 mg (n=73) %		600 mg (n=74) %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Anemia	3	0	8	1
- Thrombocytopenia	0	0	1	0
- Neutropenia	7	3	8	3
Biochemistry Parameters				
- Elevated Creatinine	0	0	3	0
- Reduced Albumin	3	0	4	0
- Elevated Bilirubin	1	0	1	3
- Elevated Alkaline Phosphatase	0	0	3	0
- Elevated SGOT (AST)	4	0	3	3
- Elevated SGPT (ALT)	6	0	7	1

¹CTC Grades: neutropenia (Grade 3 ≥ 0.5 - $1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade 3 $\geq 10 - 50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), 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)

6.12 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 reactions have been reported during clinical trials of Gleevec. These reactions are included based on clinical relevance.

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

Rare: pericarditis

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

Dermatologic: Less common: dry skin, alopecia

Infrequent: exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura, psoriasis

Rare: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome)

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

Rare: colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor necrosis, gastrointestinal perforation [*see Warnings and Precautions (5.4)*]

General Disorders and Administration Site Conditions: Rare: tumor necrosis

Hematologic: Infrequent: pancytopenia

Rare: aplastic anemia

Hepatobiliary: Infrequent: hepatitis

rare: hepatic failure

Hypersensitivity: Rare: angioedema

Infections: Infrequent: sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: Infrequent: hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased

Rare: hyperkalemia, hyponatremia

Musculoskeletal: Less common: joint swelling

Infrequent: sciatica, joint and muscle stiffness

Rare: avascular necrosis/hip osteonecrosis

Nervous System/Psychiatric: Less common: paresthesia

Infrequent: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment

Rare: increased intracranial pressure, cerebral edema (including fatalities), confusion, convulsions

Renal: Infrequent: renal failure, urinary frequency, hematuria

Reproductive: Infrequent: breast enlargement, menorrhagia, sexual dysfunction

Respiratory: Rare: interstitial pneumonitis, pulmonary fibrosis

Special Senses: Less common: conjunctivitis, vision blurred

Infrequent: conjunctival hemorrhage, dry eye, vertigo, tinnitus

Rare: macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage

Vascular Disorders: Rare: thrombosis/embolism

6.13 Postmarketing Experience

The following additional adverse reaction have been identified during post approval use of Gleevec. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In some cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome reported during post-marketing surveillance, a recurrent dermatologic reaction was observed upon re-challenge. 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.

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

7 DRUG INTERACTIONS

7.1 Agents Inducing CYP3A Metabolism

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. If alternative treatment cannot be administered, a dose adjustment should be considered. [see *Dosage and Administration* (2.9)]

7.2 Agents Inhibiting CYP3A Metabolism

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). Caution is recommended when administering Gleevec with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.

7.3 Interactions with Drugs Metabolized by CYP3A4.

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., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus.).

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 instead of warfarin.

7.4 Interactions with Drugs Metabolized by CYP2D6

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.

7.5 Interaction with Acetaminophen

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [see *Warnings and Precautions* (5.1)]

8.3 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 from Gleevec, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Gleevec safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML and in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon-alpha therapy. There are no data in children under 2 years of age. Follow-up in children with newly diagnosed Ph+ chronic phase CML is limited.

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/m² in children vs. 10.0 L/hr/m² in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Dosing in children at both 260 mg/m² and 340 mg/m² achieved an AUC similar to the 400 mg dose in adults. The comparison of AUC on Day 8 vs. Day 1 at 260 mg/m² and 340 mg/m² dose levels revealed a 1.5- and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

8.5 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 *Warnings and Precautions* (5.2)] 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.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 11) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. Patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean C_{max} /dose and AUC/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean C_{max} /dose and AUC/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. [see *Dosage and Administration* (2.10)]

Table 11 Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	>1.0-1.5x ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

8.7 Renal Impairment

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.

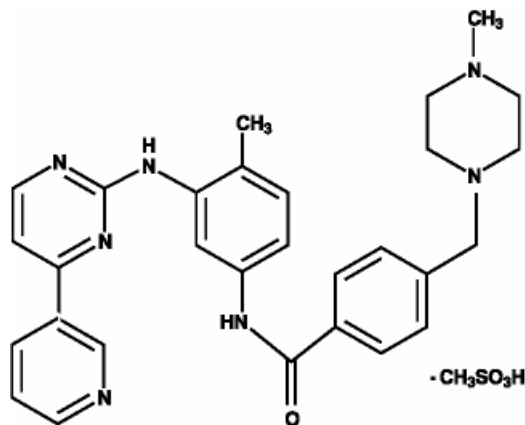
10 OVERDOSAGE

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

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

11 DESCRIPTION

Imatinib is a small molecule kinase inhibitor. Gleevec 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 $C_{29}H_{31}N_7O \cdot CH_3SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers \leq pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

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

12 CLINICAL PHARMACOLOGY

12.1 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 CML. Imatinib inhibits proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using *ex vivo* peripheral blood and bone marrow samples from CML patients.

In vivo, imatinib 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 GIST cells, which express an activating c-kit mutation.

12.3 Pharmacokinetics

The pharmacokinetics of Gleevec have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. The pharmacokinetics of Gleevec are similar in CML and GIST 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-demethyl derivative (CGP74588), are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1,000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α 1-acid glycoprotein.

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib. The plasma protein binding of N-demethylated metabolite CGP74588 is similar to that of the parent compound. 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 μ M, respectively.

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. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In the 2-year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at \geq 30 mg/kg/day. Target organs for neoplastic changes were the kidneys (renal tubule and renal pelvis), urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. Neoplastic lesions were not seen at: 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach, and 15 mg/kg/day for the preputial and clitoral gland. The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0.5 to 4 or 0.3 to 2.4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 to 3.0 times the daily exposure in children (based on AUC) at 340 mg/m². The renal tubule adenoma/carcinoma, renal pelvis transitional cell neoplasms, the urinary bladder and urethra transitional cell papillomas, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumors of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day. The relevance of these findings in the rat carcinogenicity study for humans is not known.

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, male rats were dosed for 70 days prior to mating and female rats were dosed 14 days prior to mating and through to gestational Day 6. 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 \leq 20 mg/kg (one-fourth the maximum human dose of 800 mg). The fertility of male and female rats was not affected.

In a pre- and post-natal development study in female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) from gestational Day 6 until the end of lactation, red vaginal discharge was noted on either gestational Day 14 or 15. In the first generation offspring at this same dose level, mean body weights were reduced from birth until terminal sacrifice. First generation offspring fertility was not affected but reproductive effects were noted at 45 mg/kg/day including an increased number of resorptions and a decreased number of viable fetuses.

Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperm were observed in the high dose males rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by Gleevec

Human studies on male patients receiving Gleevec and its affect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on Gleevec treatment should consult with their physician.

14 CLINICAL STUDIES

14.1 Chronic Myeloid Leukemia

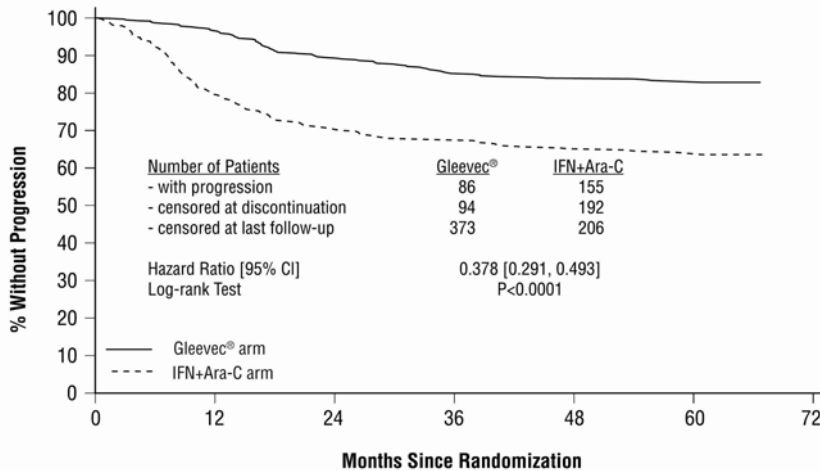
Chronic Phase, Newly Diagnosed: An open-label, multicenter, international randomized Phase 3 study has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent Gleevec or a combination of interferon- α (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6 months, a major cytogenetic response (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or severe intolerance to treatment were also allowed to cross over to the alternative treatment arm with the permission of the study monitoring committee (SMC). In the Gleevec arm, patients were treated initially with 400 mg daily. Dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m²/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m²/day for 10 days/month.

A total of 1,106 patients were randomized from 177 centers in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18-70 years), with 21.9% of patients \geq 60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% Black patients. At the cut-off for this analysis (5 years after last patient had been recruited), the median duration of first line treatment was 60 and 8 months in the Gleevec and IFN arm, respectively. The median duration of second-line treatment with Gleevec was 45 months. 69% of patients randomized to Gleevec are still

receiving first-line treatment. In these patients, the average dose of Gleevec was 382 mg ± 50 mg. Overall, in patients receiving first line Gleevec, the median daily dose delivered was 389 mg ± 71 mg. Due to discontinuations and cross-overs, only 3% of patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of consent (14%) 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 (26%) and progression (14%).

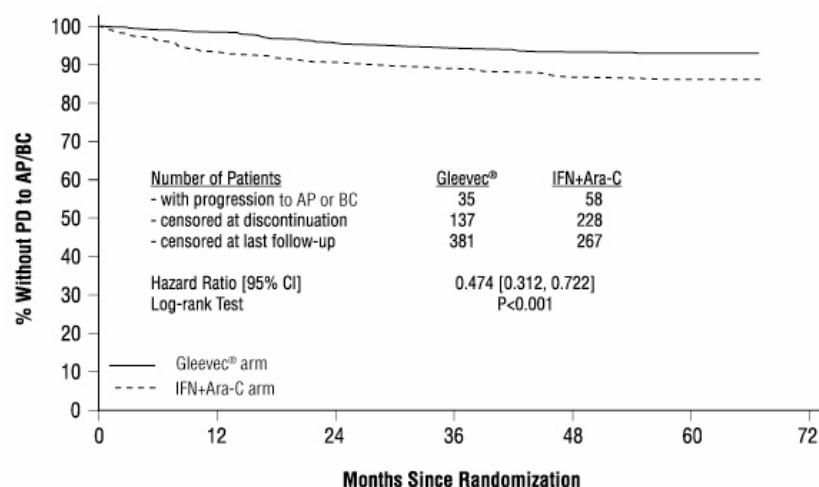
The primary efficacy endpoint of the study was progression-free survival (PFS). Progression was defined as any of the following events: progression to accelerated phase or blast crisis (AP/BC), death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. The protocol specified that the progression analysis would compare the intent to treat (ITT) population: patients randomized to receive Gleevec were compared with patients randomized to receive interferon. Patients that crossed over prior to progression were not censored at the time of cross-over, and events that occurred in these patients following cross-over were attributed to the original randomized treatment. The estimated rate of progression-free survival at 60 months in the ITT population was 83.2% [79, 87] in the Gleevec arm and 64.1% [59, 69] in the IFN arm (p<0.0001, log-rank test), (Figure 1). With 5 years follow up there were 86 (15.6%) progression events in the Gleevec arm: 35 (6.3%) progression to AP/BC, 28 (5.1%) loss of MCyR, 14 (2.5%) loss of CHR or increase in WBC and 9 (1.6%) CML unrelated deaths. In contrast, there were 155 (28.0%) events in the IFN+Ara-C arm of which 128 occurred during first-line treatment with IFN-Ara-C. The estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 60 months was 92.9% [90, 96] in the Gleevec arm compared to the 86.2%, [82, 90] (p≤0.001) in the IFN arm, (Figure 2). The annual rates of any progression events have decreased with time on therapy. The probability of remaining progression free at 60 months was 95% for patients who were in complete cytogenetic response with molecular response (≥3 log reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 89% for patients in complete cytogenetic response but without a major molecular response and 70% in patients who were not in complete cytogenetic response at this time point (p<0.001).

Figure 1
Progression Free Survival (ITT Principle)



Sponsor agreed for figure 1 only to change title to “Progression-free survival” – FDA OK

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



A total of 57 (10.3%) and 73 (13.2%) patients died in the Gleevec and IFN+Ara-C group, respectively. At 60 months the estimated overall survival is 89.4% (86, 92) vs. 85.6% (82, 89) in the randomized Gleevec and the IFN+Ara-C group, respectively (p=0.049 log-rank test). The hazard ratio is 0.71 with 95% CI 0.50-1.00. This time-to-event endpoint may be affected by the high crossover rate from IFN+Ara-C to Gleevec. Major cytogenetic response, hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 12. 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 (no cross-over data considered for evaluation of responses). Median time to CCyR in the 454 responders was 6 months (range 2-57 months, 25th to 75th percentiles = 3 to 10 months) with 10% of responses seen only after 22 months of therapy).

Table 12 Response in Newly Diagnosed CML Study (60-Month Data)

(Best Response Rate)	Gleevec n=553	IFN+Ara-C n=553
Hematologic Response¹		
CHR Rate n (%)	534 (96.6%)*	313 (56.6%)*
[95% CI]	[94.7%, 97.9%]	[52.4%, 60.8%]
Cytogenetic Response²		
Major Cytogenetic Response n (%)	471 (85.2%)*	93 (16.8%)*
[95% CI]	[81.9%, 88.0%]	[13.8%, 20.2%]
Unconfirmed ³	88.6%*	23.3%*
Complete Cytogenetic Response n (%)	404 (73.1%)*	35 (6.3%)*
Unconfirmed ³	82.1%*	11.6%*

* p<0.001, Fischer's exact test

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

WBC<10 x 10⁹/L, platelet <450 x 10⁹/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, 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.

Molecular response was defined as follows: in the peripheral blood, after 12 months of therapy, reduction of ≥3 logarithms in the amount of bcr-abl transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline. Molecular response was only evaluated in a subset of patients who had a complete cytogenetic response by 12 months or later (N = 333). The molecular response rate in patients who had a complete cytogenetic response in the Gleevec arm was 59% at 12 months and 72% at 24 months.

Physical, functional, and treatment-specific biologic response modifier scales from the FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier) instrument were used to assess patient-reported general effects of interferon toxicity in 1,067 patients with CML in chronic phase. After one month of therapy to six months of therapy, there was a 13%-21% decrease in median index from baseline in patients treated with interferon, consistent with increased symptoms of interferon toxicity. There was no apparent change from baseline in median index for patients treated with Gleevec.

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

Chronic Phase, Prior Interferon-Alpha Treatment: 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon: failure to achieve (within 6 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses $\geq 25 \times 10^6$ 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 13. 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: $\geq 15\%$ - $<30\%$ blasts in PB or BM; $\geq 30\%$ blasts + promyelocytes in PB or BM; $\geq 20\%$ basophils in PB; and $<100 \times 10^9/L$ 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 13. 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 $\geq 30\%$ 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 13. The hematologic response rate was higher in untreated patients than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major cytogenetic response rate was also higher for the 600 mg dose group than for the 400 mg dose group (17% vs. 8%).

Table 13 Response in CML Studies

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
	400 mg	600 mg n=158 400 mg n=77	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 (Unconfirmed ³)	60% [55.3–63.8] (65%)	21% [16.2–27.1] (27%)	7% [4.5–11.2] (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 $<10 \times 10^9/L$, platelet $<450 \times 10^9/L$, 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 $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, no blood blasts, BM blasts $<5\%$ and no extramedullary disease]

NEL: Same criteria as for CHR but ANC $\geq 1 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$ (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.

³Unconfirmed 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.

⁴Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least 1 month after the initial bone marrow study.

The median time to hematologic response was 1 month. In late chronic phase CML, with a median time from diagnosis of 32 months, an estimated 87.8% of patients who achieved MCyR maintained their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [88.3, 93.2]. In accelerated phase, median duration of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5 months for 400 mg). 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. 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.

14.2 Pediatric CML

A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients were treated with Gleevec 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients after 8 weeks of therapy. The complete cytogenetic response rate (CCyR) was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months.

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. Patients ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m²/day (n=3), 340 mg/m²/day (n=4), 440 mg/m²/day (n=5) and 570 mg/m²/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had a minimal cytogenetic response.

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

14.3 Acute Lymphoblastic Leukemia

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

Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 14. The median duration of hematologic response was 3.4 months and the median duration of MCyR was 2.3 months.

Table 14: Effect of Gleevec on Relapsed/Refractory Ph+ ALL.

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

14.4 Myelodysplastic/Myeloproliferative Diseases

An open label, multicenter, phase 2 clinical trial was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These patients were treated with Gleevec 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received Gleevec at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response). Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene re-arrangement. All of these patients responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1(7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in table 15. Response durations of phase 2 study patients ranged from 141+ days to 457+ days.

Table 15: Response in MDS/MPD

	Complete Hematologic Response	Major Cytogenetic Response

	N	Complete Hematologic Response	Major Cytogenetic Response
		N (%)	N (%)
Overall Population	31	14 (45)	12 (39)
Chromosome 5 Translocation	14	11 (79)	11 (79)
Chromosome 4 Translocation	2	2 (100)	1 (50)
Others / no Translocation	14	1 (7)	0 (0)
Molecular Relapse	1	NE ¹	NE ¹

¹NE: Not Evaluable

14.5 Aggressive Systemic Mastocytosis

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

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

Of the 28 patients treated for ASM, 8 (29%) achieved a complete hematologic response and 9 (32%) a partial hematologic response (61% overall response rate). Median duration of Gleevec therapy for the 5 ASM patients in the phase 2 study was 13 months (range 1.4-22.3 months) and between 1 month and more than 30 months in the responding patients described in the published medical literature. A summary of the response rates to Gleevec in ASM is provided in Table 16. Response durations of literature patients ranged from 1+ to 30+ months.

Table 16 Response in ASM

Cytogenetic Abnormality	Number of Patients	Complete Hematologic response	Partial Hematologic response
		N (%)	N (%)
FIP1L1-PDGFR α Fusion Kinase (or CHIC2 deletion)	7	7(100%)	0%
Juxtamembrane Mutation	2	0 (0%)	2 (100%)
Unknown or No Cytogenetic Abnormality detected	15	0(0%)	7 (44%)
D816V Mutation	4	1* (25%)	0%
Total	28	8 (29%)	9 (32%)

*Patient had concomitant CML and ASM

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

14.6 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

One open-label, multicenter, phase 2 study was conducted testing Gleevec in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 14 patients with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia (HES/CEL). HES patients were treated with 100 mg to 1000 mg of Gleevec daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series. These patients received Gleevec at doses of 75 mg to 800 mg daily. Hematologic response rates are summarized in Table 17. Response durations for literature patients ranged from 6+ weeks to 44 months.

Table 17: Response in HES/CEL

Cytogenetic Abnormality	Number of Patients	Complete Hematological Response	Partial Hematological Response
		N (%)	N (%)
Positive FIP1L1-PDGFR α Fusion Kinase	61	61 (100%)	0%
Negative FIP1L1-PDGFR α Fusion Kinase	56	12 (21%)	9 (16%)
Unknown Cytogenetic Abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	23 (13%)

14.7 Dermatofibrosarcoma Protuberans

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

An open-label, multicenter, phase 2 study was conducted testing Gleevec in a diverse population of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with Gleevec 800 mg daily (age range 23 to 75 years). DFSP was metastatic, locally recurrent following initial surgical resection and not considered amenable to further surgery at the time of study entry. A further 6 DFSP patients treated with Gleevec are reported in 5 published case reports, their ages ranging from 18 months to 49 years. The total population treated for DFSP therefore comprises 18 patients, 8 of them with metastatic disease. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Gleevec daily. A single pediatric patient received 400 mg/m²/daily, subsequently increased to 520 mg/m²/daily. Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. Responses to treatment are described in Table 18.

Table 18 Response in DFSP

	Number of Patients (n=18)	%
Complete Response	7	39
Partial Response *	8	44
Total Responders	15	83

* 5 patients made disease free by surgery

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

14.8 Gastrointestinal Stromal Tumors

One open-label, multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study, 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 36 months. The study was not powered to show a statistically significant difference in response rates between the 2 dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit (CD117) positive unresectable and/or metastatic malignant GIST. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex method after antigen retrieval.

The primary outcome of the study was objective response rate. Tumors were required to be measurable at entry in at least one site of disease, and response characterization was based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 19.

Table 19 Tumor Response in GIST Trial

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

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

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society

16 HOW SUPPLIED/STORAGE AND HANDLING

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

100 mg Tablets

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

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

400 mg Tablets

Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “400” on one side with score on the other side, and “SL” on each side of the score.

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

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

Dispense in a tight container, USP.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing and Administration

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or to stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose they should be advised to take their dose as soon as possible unless it is almost time for their next dose in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose. Patients should be advised to take Gleevec with a meal and a large glass of water.

17.2 Pregnancy and Breast Feeding

Patients should be advised to inform their doctor if they are or think they may be pregnant. Patients should also be advised not to breast feed while taking Gleevec.

17.3 Adverse Reactions

Patients should be advised to tell their doctor if they experience side effects during Gleevec therapy including fever, shortness of breath, blood in their stools, jaundice, sudden weight gain ,symptoms of cardiac failure, or if they have a history of cardiac disease or risk factors for cardiac failure.

17.4 Drug Interactions

Patients should be advised not to take any other medications, including over-the-counter medications such as acetaminophen or herbal products without talking to their doctor or pharmacist first. Examples of other medications that should not be taken with Gleevec are warfarin, erythromycin, and phenytoin . Patients should also be advised to tell their doctor if they are taking or plan to take iron supplements. Patients should also avoid grapefruit juice and other foods known to inhibit CYP3A4 while taking Gleevec.



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Stein, Switzerland

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