

**PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION**

PrGLEEVEC®

imatinib mesylate Tablets

imatinib 100 mg and 400 mg Tablets

Protein kinase inhibitor

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GLEEVEC is a registered trademark

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Pr**GLEEVEC**[®]
imatinib mesylate

PART I: HEALTH PROFESSIONAL INFORMATION
SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets 100 mg and 400 mg	Coating: ferric oxide (red), ferric oxide (yellow). <i>For a complete listing see Dosage Forms, Composition section.</i>

INDICATIONS AND CLINICAL USE

- GLEEVEC (imatinib mesylate) is indicated for the treatment of adult patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase.

Clinical effectiveness in newly diagnosed CML was based on progression-free survival, hematologic and cytogenetic response rates (surrogate endpoints) that are reasonably likely to predict clinical benefit in a long-term randomized controlled study.

- GLEEVEC (imatinib mesylate) is indicated for the treatment of pediatric patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase.

Clinical effectiveness in newly diagnosed CML, was based on hematologic and cytogenetic response rates (surrogate endpoints) in a short-term uncontrolled study in which the majority of patients withdrew from protocol therapy to undergo hematopoietic stem cell transplantation.

- GLEEVEC is also indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML) in blast crisis or accelerated phase, or in chronic phase after failure of interferon- alpha therapy.

Clinical effectiveness in Philadelphia chromosome-positive chronic myeloid leukemia in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy) was based on hematologic and cytogenetic response rates (surrogate endpoints), which have shown to be sustained for at least two years.

- GLEEVEC is also indicated for use as a single agent for induction phase therapy in

adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL).

Clinical effectiveness for use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) was based on hematologic response rates (surrogate endpoints).

- GLEEVEC is also indicated for the treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.

Clinical effectiveness in adult patients with relapsed or refractory Ph+ ALL as monotherapy was based on hematologic and cytogenetic response rates (surrogate endpoints).

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

Clinical effectiveness in adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements was based on hematologic and cytogenetic response rates (surrogate endpoints).

- GLEEVEC is also indicated for the treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD¹) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD¹ is not known or unavailable, treatment with GLEEVEC may be considered if there is no satisfactorily response to other therapies.

Clinical effectiveness in adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD¹) without the D816V c-Kit mutation and in adult patients with ASM or SM-AHNMD¹ where c-Kit mutational status is not known or unavailable, and if there is no satisfactory response to other therapies was based on hematologic response rates (surrogate endpoints).

¹ ASM: Aggressive systemic mastocytosis; SM-AHNMD: Systemic mastocytosis with an associated clonal hematological non-mast-cell disorder.

- GLEEVEC is also indicated for the treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFR α rearrangement.

Clinical effectiveness in adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFR α rearrangement was based on hematologic and cytogenetic response rates (surrogate endpoints).

- GLEEVEC is also indicated for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

Clinical effectiveness in adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) was based on objective response rate (surrogate endpoints).

- GLEEVEC is also indicated for the treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Clinical effectiveness in gastrointestinal stromal tumors (GIST) was based on objective response rates (surrogate endpoints) that are reasonably likely to predict clinical benefit. There are no controlled trials demonstrating clinical benefit such as improvement in disease-related symptoms or increased survival.

- GLEEVEC is also indicated for the adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST.

Clinical effectiveness in the adjuvant GIST indication was based on recurrence free survival after one year of adjuvant therapy. The optimal treatment duration with GLEEVEC is not known. Overall survival data are not available.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Severe congestive heart failure (CHF) and reduction of left ventricular ejection fraction (LVEF) have been observed (see “Cardiovascular” section under WARNINGS and PRECAUTIONS).
- Rhabdomyolysis has been rarely observed. (See “Adverse Reactions from Post-Marketing reports” section under ADVERSE REACTIONS).
- Severe hemorrhages may occur (See “Hemorrhage” section under WARNINGS and PRECAUTIONS).

- Fluid retention may occur (See “Fluid Retention” section under WARNINGS AND PRECAUTIONS).
- Liver failure (in some cases, fatal) may occur (See “Hepatic/Biliary/Pancreatic” section under WARNINGS AND PRECAUTIONS).
- Gastrointestinal perforation (in some cases, fatal) may occur (See “Gastrointestinal” section under WARNINGS AND PRECAUTIONS).

GLEEVEC should only be administered under the supervision of a physician experienced with the use of chemotherapy and with treatment of hematological malignancies and/or malignant sarcomas including gastrointestinal stromal tumors (GISTs) and dermatofibrosarcoma protuberans (DFSP).

General

Effects on ability to drive and use machines

Reports of motor vehicle accidents have been received in patients receiving GLEEVEC. Caution should be recommended when driving a car or operating machinery (see Adverse Reactions from Post-Marketing reports section and Drug-Lifestyle Interactions section).

Tumour Lysis Syndrome (TLS): Tumor lysis syndrome has occurred in patients taking GLEEVEC, including fatal cases (see “Adverse Reactions from Post-marketing Reports”). Patients at increased risk for TLS include those with tumours having a high proliferative rate (e.g. CML-blast crisis), concomitant chemotherapy or radiotherapy or having a solid tumour of large size (bulky disease), decreased kidney function or elevated lactate dehydrogenase (LDH) at baseline. Preventative measures, including correction of clinically significant dehydration and treatment of high uric acid levels, should be considered for patients at increased risk of developing TLS (see DOSAGE AND ADMINISTRATION and Monitoring and Laboratory Tests).

Carcinogenesis and Mutagenesis

A 2-year preclinical carcinogenicity study conducted in rats demonstrated renal adenomas/carcinomas, urinary bladder and urethra papillomas, papillomas/carcinomas of the preputial and clitoral gland, adenocarcinomas of the small intestine, adenomas of the parathyroid glands, benign and malignant tumors of the adrenal medulla and papillomas/carcinomas of the nonglandular stomach (See TOXICOLOGY).

Long-term, non-neoplastic histological changes identified in the preclinical carcinogenicity study in rats include cardiomyopathy.

The relevance of these findings in the rat carcinogenicity study for humans is not known. An analysis of the clinical safety data from clinical trials and spontaneous adverse event reports did not provide evidence of an increased overall incidence of malignancies in patients treated with imatinib mesylate compared to that of the general population.

However, adverse events in cancer patients are significantly under reported and a large proportion of patients treated with GLEEVEC have had limited follow-up thus not permitting a

final analysis of the potential for an increased incidence of a secondary malignancy in patients treated with GLEEVEC.

Cardiovascular

Severe congestive heart failure (CHF) and reduction of left ventricular ejection fraction (LVEF) have been reported in patients taking GLEEVEC. Although several of these patients had pre-existing conditions including hypertension, diabetes and prior coronary artery disease, they were subsequently diagnosed with CHF. Patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully and those with symptoms or signs consistent with CHF should be evaluated and treated. In patients with history of cardiac disease or in elderly patients, a baseline evaluation of LVEF is recommended prior to initiation of GLEEVEC therapy.

In patients with hypereosinophilic syndrome (HES) with occult or known infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction believed to be associated with HES cell degranulation upon initiation of GLEEVEC therapy, have been reported. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding GLEEVEC. Myelodysplastic/myeloproliferative diseases (MDS/MPD) and systemic mastocytosis (SM) might 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 and SM-AHNMD associated with high eosinophil levels. These patients with HES/CEL or ASM, SM-AHNMD and MDS/MPD must be also on 1-to 2 mg/kg of prednisone equivalent oral steroids for one to two weeks, initiated at least 2 days prior to beginning GLEEVEC therapy.

Endocrine and Metabolism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. Thyroid-Stimulating Hormone (TSH) levels should be closely monitored in such patients.

Fluid Retention and edema

GLEEVEC (imatinib mesylate) is often associated with edema and occasionally serious fluid retention (see **ADVERSE REACTIONS Tables 1 and 2**). All Grades of fluid retention/edema were reported in up to 61.7% for newly diagnosed CML patients, up to 76.2% for other CML patients across all clinical trials, and up to 80.3% for GIST patients. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention as fluid retention can occur after months of treatment. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher imatinib dose. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking GLEEVEC and in 2.1% to 5.8% of other adult CML patients taking GLEEVEC. In addition, other severe fluid retention events (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) were reported in 1.3% of newly diagnosed CML patients taking GLEEVEC and in 1.7% to 6.2% of other adult CML patients taking GLEEVEC.

Gastrointestinal

*Hemorrhage: See “**Hemorrhage**” below.*

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.

Hematologic

Hematologic Toxicity: Treatment with GLEEVEC is often associated with neutropenia or thrombocytopenia (See ADVERSE REACTIONS, Tables 8 to 11). 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). 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 involving neutropenia (31%), thrombocytopenia (16%) and anemia (14%). These generally occur within the first several months of therapy (See DOSAGE AND ADMINISTRATION).

An increased rate of opportunistic infections was observed in a monkey study with chronic imatinib treatment. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans, where all grades of lymphopenia were observed in 0.3% patients).

Hemorrhage

All Grades of hemorrhage were reported in up to 28.9% for newly diagnosed CML patients, up to 53% for other CML patients across all clinical trials, and up to 29.9% for GIST patients.

In the newly diagnosed CML trial, 1.8% of patients had Grades 3/4 hemorrhage. In the unresectable and/or metastatic malignant GIST clinical trial (B2222) eight patients (5.4%, five patients in the 600 mg dose group and three patients in the 400 mg dose group) were reported to have had gastrointestinal (GI) bleeds or intra-tumoral bleeds. Four patients with intra-tumoral bleeds had either intra-abdominal or intra-hepatic, depending on the anatomical location of the tumor lesions. One patient, who had a history of GI bleeding prior to the study, died due to gastrointestinal bleeding.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI hemorrhage, has been reported in post-marketing experience in patients with CML, GIST, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with GLEEVEC. When needed, GLEEVEC discontinuation may be considered. Time to GAVE diagnosis was commonly reported at about 1 year of exposure but was variable (6 days to 7 years) after starting treatment with GLEEVEC (see ADVERSE REACTIONS).

Subdural hematomas have been reported in association with imatinib administration in patients with other contributing factors, including older age (e.g., age greater than 50-55 years); thrombocytopenia due to the underlying malignancy or concomitant administration of multi-agent chemotherapy; concomitant administration of medications that increase bleeding risk; and

prior lumbar puncture or head trauma. In clinical trials, the incidence of subdural hematoma has ranged from 0 to 2.4%.

This risk of bleeding should be evaluated carefully in all patients. Caution should be exercised with the concomitant use of antiplatelet agents or warfarin, especially in patients who are thrombocytopenic. Platelet counts and prothrombin time should be measured on a regular basis when imatinib is used concurrently with anticoagulants, prostacyclins, or other medications that increase bleeding risk. Patients who experience head trauma or have unexplained neurological symptoms should be evaluated for subdural hematoma. In view of a potential interaction between GLEEVEC and warfarin leading to increased exposure to warfarin, patients who require anticoagulation with warfarin should be monitored especially closely when GLEEVEC dose adjustments are necessary (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

Liver failure: There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some cases the outcome was fatal. One patient, who was taking acetaminophen regularly for fever along with GLEEVEC, died of acute liver failure (See DRUG INTERACTIONS).

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with GLEEVEC (see ADVERSE REACTIONS Tables 1, 2 and 5). 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 sections ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION). Patients with hepatic impairment should be closely monitored. Although pharmacokinetic analysis results showed there is considerable inter-subject variation, the mean exposure to imatinib did not differ significantly between patients with mild and moderate liver dysfunction (as measured by dose normalized AUC) and patients with normal liver function. Patients with severe liver dysfunction demonstrated increased exposure to imatinib and its active metabolite CGP 74588. Liver function monitoring remains crucial as no long term toxicity and tolerability have been established (See CLINICAL PHARMACOLOGY).

In GIST patients with liver metastases, exposure to GLEEVEC may be higher than in CML patients, due to impaired liver function (See ADVERSE REACTIONS).

Hepatotoxicity has been observed in patients treated with GLEEVEC. All Grades of liver toxicity (including liver failure) were reported in up to 11.6% for newly diagnosed CML patients, up to 12% for other CML patients across all clinical trials, and up to 12.2% for unresectable and/or metastatic malignant GIST patients.

Toxicities From Long-Term Use: It is important to consider potential toxicities suggested by animal studies, specifically, *liver kidney and cardiac toxicity, and immunosuppression*. Liver toxicity was observed in rats, dogs and cynomolgus monkeys in repeated dose studies. Most severe toxicity was noted in dogs and included elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia.

Immune

Hepatitis B virus reactivation

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving a Bcr-Abl tyrosine kinase inhibitor (TKI), including GLEEVEC. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for HBV infection before initiating treatment with GLEEVEC. Patients currently on GLEEVEC should have baseline testing for HBV infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with GLEEVEC should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Renal

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.

GLEEVEC and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics.

In patients with impaired renal function, GLEEVEC plasma exposure is higher (1.5- to 2-fold increase) than in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), a GLEEVEC-binding protein, in patients with renal dysfunction. As well, there is a significant correlation in the incidence of serious adverse events with decreased renal function ($p=0.0096$). Patients with mild or moderate renal impairment should be treated with caution (see DOSAGE AND ADMINISTRATION). Since the effect of GLEEVEC treatment on patients with severe renal dysfunction or on dialysis has not been sufficiently assessed, recommendations on the treatment of these patients with GLEEVEC cannot be made. Patients with history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with renal failure should be evaluated and treated.

Long term treatment with GLEEVEC may result in declines in renal function. Patients treated with imatinib in clinical studies had a decrease over time in estimated glomerular filtration rate (eGFR). Treatment-naïve patients with newly-diagnosed CML initiated on imatinib among three Phase III trials showed a decline in eGFR from a median baseline value of 100.1 ml/min/1.73m² (N=1279) to 93.5 ml/min/1.73m² at 6 months (N=1213), 92.8 ml/min/1.73m² at 1 year (N=1161) and 85.5 ml/min/1.73m² at 5 years (N=585). Monitoring for renal function should be undertaken before initiating therapy and periodically thereafter.

Respiratory

Pulmonary events: Rare cases of pulmonary fibrosis and interstitial pneumonitis have been reported in patients who have received GLEEVEC. However, no definitive relationship has been established between the occurrence of these pulmonary events and treatment with GLEEVEC.

Skin

Skin and Mucosa: Although rare, **Erythema multiforme** (EM), Toxic epidermal Necrolysis (TEN) and **Stevens Johnson** syndrome (SJS) have been reported in patients who have received GLEEVEC. Skin biopsies in some cases of exfoliative skin rash associated with GLEEVEC use have shown a mixed cellular infiltrate characteristic of a toxic drug reaction. Severe cases of exfoliative rash may require treatment interruption or discontinuation.

Drug reaction with eosinophilia and systemic symptoms (DRESS), a potentially life-threatening syndrome including fever, severe skin eruption, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement, has also been reported in GLEEVEC-treated patients. DRESS regressed when GLEEVEC was discontinued, and in all cases where the drug was re-introduced, DRESS recurred. If DRESS occurs, GLEEVEC should be interrupted, and permanent discontinuation should be considered.

Special Populations:

Female Patients of Reproductive Potential:

Females of reproductive potential should be advised to use effective birth control (methods that result in less than 1 % pregnancy rates) when using GLEEVEC during treatment and for at least 15 days after stopping treatment with GLEEVEC (See Pregnant Women).

Females of reproductive potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml within 1 week prior to initiating GLEEVEC.

Pregnant Women:

GLEEVEC can cause fetal harm when administered to a pregnant woman. Teratogenicity and significant post-implantation loss have been observed in rat studies (See TOXICOLOGY). There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken GLEEVEC. There are no clinical trials on the use of GLEEVEC in pregnant women.

GLEEVEC should not be administered to pregnant women. Patients should advise their physician if they are pregnant. If it is used during pregnancy the patient should be apprised of the potential risk to the fetus.

Nursing Women:

Imatinib and its active metabolite can be excreted into breast milk in humans and in animals. There are cases of imatinib exposure during lactation in humans including one case reported the milk: plasma ratio of 0.5 for imatinib and 0.9 for the metabolite. Since the effects of exposure of the infant to imatinib are potentially serious, women should not breast feed during treatment and for at least 15 days after stopping treatment with GLEEVEC.

Male fertility:

Stem cell factor and c-Kit genes are known to be important for germ cell development. Human studies on male patients receiving GLEEVEC and its effect on male fertility and spermatogenesis have not been performed. However, clinical evidence of profound oligospermia with GLEEVEC use has been reported in the literature as has clinical evidence for maintained male fertility. There is also pre-clinical evidence of impaired spermatogenesis, lower testes and epididymal weights as well as a reduced number of motile sperm without a reduction in fertility (See TOXICOLOGY). Therefore, physicians should advise and counsel their male patients as appropriate.

Pediatrics:

There is no experience with the use of GLEEVEC in pediatric patients with CML under 2 years of age. There is very limited to no experience with the use of GLEEVEC in pediatric patients in other indications.

There have been case reports of growth retardation in children and pre-adolescents receiving GLEEVEC. No prospective studies have been carried out in this regard and the long term effects of prolonged treatment with GLEEVEC on growth in pediatric patients are unknown. In a juvenile toxicology study, an impact on growth and a delay in sexual maturation were observed in rats (see TOXICOLOGY, Juvenile Toxicology). Therefore, close monitoring of growth in children under GLEEVEC treatment is highly recommended.

Geriatrics (65 years or above):

In the CML phase II studies, approximately 20% of patients were older than 65 years. The efficacy of GLEEVEC was similar in all age groups studied.

In the adjuvant GIST study, 221 patients (31%) were older than 65 years. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients. The efficacy of GLEEVEC was similar in patients older than 65 years and younger patients.

Monitoring and Laboratory tests:

Patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully and those with symptoms or signs consistent with CHF should be evaluated and treated. In patients with history of cardiac disease or in elderly patients, a baseline evaluation of LVEF is recommended prior to initiation of GLEEVEC therapy (see Cardiovascular).

For patients receiving GLEEVEC, 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) (see Hematologic and DOSAGE and ADMINISTRATION).

Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated (see Hepatic/Biliary/Pancreatic and DOSAGE and ADMINISTRATION).

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention as fluid retention can occur after months of treatment with GLEEVEC (see Fluid Retention and edema).

Thyroid-Stimulating Hormone (TSH) levels should be closely monitored in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC (see Endocrine and Metabolism).

Signs and symptoms consistent with tumour lysis syndrome (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, elevated LDH, high fevers) should be monitored at baseline and during initial treatment with GLEEVEC (see Tumour Lysis Syndrome (TLS) and DOSAGE AND ADMINISTRATION).

Close monitoring of growth in children under GLEEVEC treatment is highly recommended (see Special Populations, Pediatrics).

During treatment with GLEEVEC serum electrolytes should be regularly monitored for possible hypophosphatemia, hyperkalemia, and hyponatremia in all patients as well as glucose, blood urea nitrogen (BUN) and creatinine. In addition, in pediatric patients, serum calcium and albumin should also be regularly monitored. Grades 3/4 hypophosphatemia have been observed in 16.5% (15% Grade 3 and 1.5% Grade 4) of patients in a phase I dose finding study 03001 (N=143) and a phase II study 0102 (N=260) of chronic myeloid leukemia in blast crisis.

In patients with CML, regular response monitoring, particularly when therapy is modified, is essential to detect early signs of loss of response so that appropriate actions can be taken to avoid disease progression. A loss of response can occur at any time, but is more likely when imatinib treatment is modified (See DOSAGE AND ADMINISTRATION).

Females of reproductive potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml within 1 week prior to beginning therapy (see Special Populations).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

GLEEVEC (imatinib mesylate) was generally well tolerated across all studies in CML and GIST. Complications of advanced malignancies and co-administered medications make causality of adverse events difficult to assess in single arm studies. The majority of GLEEVEC-treated patients experienced adverse events at some time.

Recent published literature revealed cases of musculoskeletal pain symptoms occurring upon imatinib discontinuation following long-term treatment, with a high frequency of 18% to 46% in CML patients. Those events may persist for months and were referred to as imatinib withdrawal symptoms (IWS).

Clinical Trial Adverse Drug Reactions

Chronic Myeloid Leukemia

GLEEVEC was generally well tolerated with chronic oral daily dosing in patients with CML including pediatric patients. The majority of patients experienced adverse events at some point in time, however, most events were of mild to moderate Grade. In adult clinical trials, drug discontinuation for drug-related adverse events was observed in 2.4% of newly diagnosed patients, in 5 % of patients in chronic phase, 8% in accelerated phase and 9% in blast crisis.

The most frequently reported drug-related adverse events were fluid retention (superficial edema and other fluid retention events), nausea, vomiting, diarrhea, muscle cramps, fatigue and rash (Refer to Table 1 and 2 for newly diagnosed CML and other CML patients, respectively). Superficial edemas were a common finding in all studies described primarily as periorbital edemas or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of GLEEVEC. (See DOSAGE AND ADMINISTRATION.)

Other adverse events such as pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema may be collectively described as “other fluid retention events”. These events were usually managed by withholding GLEEVEC treatment temporarily and/or with diuretics and/or other appropriate supportive care measures. However, a few of these events may be serious or life threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. The following tables list the adverse experiences which occurred in $\geq 10\%$ of patients in the clinical trials, regardless of relationship to therapy.

Table 1 Adverse experiences Regardless of Relationship to Study Drug reported in newly diagnosed CML ($\geq 10\%$ of all patients)⁽¹⁾

Adverse event (preferred term)	All Grades		CTC Grades 3/4	
	GLEEVEC N=551 (%)	IFN+Ara-C N=533 (%)	GLEEVEC N=551 (%)	IFN+Ara-C N=533 (%)
Any event	99.1	99.6	57.2	77.3
Gastrointestinal disorders				
Nausea	49.5	61.5	1.3	5.1
Diarrhea	45.4	43.3	3.3	3.2
Abdominal pain	36.5	25.9	4.2	3.9
Vomiting	22.5	27.8	2.0	3.4
Dyspepsia	18.9	8.3	0	0.8
Constipation	11.4	14.4	0.7	0.2
Dry mouth	2.9	10.9	0	0.2
General disorders and administration site conditions				
Fluid retention	61.7	11.1	2.5	0.9
- Superficial edema	59.9	9.6	1.5	0.4
- Other fluid retention events	6.9	1.9	1.3	0.6
Fatigue	38.8	67.0	1.8	25.1
Pyrexia	17.8	42.6	0.9	3.0
Rigors	9.3	34.0	0.2	0.8
Asthenia	8.0	16.9	0.2	3.8
Influenza like illness	7.3	15.9	0	0.9
Mucosal inflammation	1.1	10.3	0	3.2
Hepatobiliary disorders				
Liver toxicity (including liver failure)	11.6	17.3	4.0	5.1
Infections and infestations				
Nasopharyngitis	30.5	8.8	0	0.4
Upper respiratory tract infection	21.2	8.4	0.2	0.4
Influenza	13.8	6.2	0.2	0.2
Sinusitis	11.4	6.0	0.2	0.2
Investigations				
Weight increased	15.6	2.6	2.0	0.4
Weight decreased	5.1	17.3	0.4	1.3
Metabolic and nutritional disorders				
Anorexia	7.1	31.7	0	2.4
Musculoskeletal. & connective tissue disorders				
Muscle cramps	49.2	11.8	2.2	0.2
Musculoskeletal pain	47.0	44.8	5.4	8.6
Joint pain	31.4	38.1	2.5	7.7
Myalgia	24.1	38.8	1.5	8.3
Bone pain	11.3	15.6	1.6	3.4
Nervous system disorders				
Headache	37.0	43.3	0.5	3.8
Dizziness	19.4	24.4	0.9	3.8

Psychiatric disorders				
Depression	14.9	35.8	0.5	13.1
Insomnia	14.7	18.6	0	2.3
Anxiety	9.6	11.8	0.5	2.6
Respiratory disorders				
Cough	20.0	23.1	0.2	0.6
Pharyngolaryngeal pain	18.1	11.4	0.2	0
Dyspnea	9.3	14.4	1.8	1.7
Skin and subcutaneous disorders				
Rash and related terms	40.1	26.1	2.9	2.4
Night sweats	9.8	15.8	0.2	0.4
Pruritus	9.8	11.8	0.2	0.2
Sweating increased	5.8	14.8	0.2	0.4
Alopecia	4.9	22.3	0	0.6
Vascular disorders				
Hemorrhage	28.9	21.2	1.8	1.7
- GI hemorrhages	1.6	1.1	0.5	0.2
- CNS hemorrhages	0.2	0.4	0	0.4

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

Table 2 Adverse Experiences Regardless of Relationship to Study Drug Reported in Other CML Clinical Trials ($\geq 10\%$ of All patients in any trial)⁽¹⁾

System Affected	Myeloid blast crisis N=260 (%)		Accelerated phase N=235 (%)		Chronic phase IFN failure N=532 (%)	
	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4
Gastrointestinal disorders						
Nausea	71	5	73	5	63	3
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Abdominal pain [¥]	30	6	33	4	32	1
Constipation	16	2	16	0.9	9	0.4
Dyspepsia	12	0	22	0	27	0
General disorders and administration site conditions						
Fluid retention [¥]	72	11	76	6	69	4
- Superficial edemas [¥]	66	6	74	3	67	2
- Other fluid retention events ^{2¥}	22	6	15	4	7	2
Pyrexia	41	7	41	8	21	2
Fatigue	30	4	46	4	48	1
Asthenia	18	5	21	5	15	0.2
Rigors	10	0	12	0.4	10	0
Chest pain	7	2	10	0.4	11	0.8
Hepatobiliary disorders						
Liver toxicity (including liver failure)	10	5	12	6	6	3
Infections and infestations						

Nasopharyngitis	10	0	17	0	22	0.2
Pneumonia NOS	13	7	10	7	4	1
Upper respiratory tract infection NOS	3	0	12	0.4	19	0
Sinusitis NOS	4	0.4	11	0.4	9	0.4
Influenza	0.8	0.4	6	0	11	0.2
Investigations						
Weight increase	5	1	17	5	32	7
Metabolic and nutritional disorders						
Anorexia	14	2	17	2	7	0
Hypokalemia	13	4	9	2	6	0.8
Musculoskeletal. & connective tissue disorders						
Musculoskeletal pain [‡]	42	9	49	9	38	2
Muscle cramps [‡]	28	1	47	0.4	62	2
Joint pain (Arthralgia) [‡]	25	5	34	6	40	1
Myalgia	9	0	24	2	27	0.2
Nervous system disorders						
Headache	27	5	32	2	36	0.6
Dizziness	12	0.4	13	0	16	0.2
Psychiatric disorders						
Insomnia	10	0	14	0	14	0.2
Anxiety	8	0.8	12	0	8	0.4
Respiratory disorders						
Dyspnea NOS	15	4	21	7	12	0.9
Cough	14	0.8	27	0.9	20	0
Pharyngitis	10	0	12	0	15	0
Skin and subcutaneous disorders						
Rash and related terms [‡]	36	5	47	5	47	3
Night sweats	13	0.8	17	1	14	0.2
Pruritis	8	1	14	0.9	14	0.8
Vascular disorders						
Hemorrhages [‡]	53	19	49	11	30	2
- CNS hemorrhages [‡]	9	7	3	3	2	1
- GI hemorrhages [‡]	8	4	6	5	2	0.4

[‡] Grouped events

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

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

Adverse Reactions in the Pediatric Population

The overall safety profile of GLEEVEC treatment in 93 pediatric patients was similar to that observed in studies with adult patients. Nausea, vomiting were the most commonly reported individual adverse events with an incidence similar to that seen in adult patients. Although most patients experienced adverse events at some time during the studies, the incidence of Grade 3/4 adverse events was low.

Significantly higher frequencies of hypocalcemia (23.5 vs 1.1%), hyperglycemia (19.6 vs 2.9%), hypoglycemia (21.6 vs 1.5%), hypophosphatemia (19.6 vs 3.3%), hypoalbuminemia (13.7 vs 0.2%) and hyponatremia (13.7 vs 0.2%) were observed in pediatric patients compared to adult patients.

Acute Lymphoblastic Leukemia:

The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported non-hematologic drug-related adverse events were fluid retention (superficial edema and other fluid retention events), nausea, vomiting, diarrhea, muscle cramps, fatigue and rash. Superficial edemas were a common finding in all studies described primarily as periorbital edemas or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of GLEEVEC (See DOSAGE AND ADMINISTRATION).

Myelodysplastic/Myeloproliferative Diseases:

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with GLEEVEC for MDS/MPD in Trial B2225, are shown in Table 3.

Table 3 Adverse Experiences Regardless of Relationship to Study Drug Reported (more than one patient) in MDS/MPD Patients in Trial B2225 (≥10% all patients) all Grades

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

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

All ASM patients experienced at least one adverse event at some time. The most frequently reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritis, rash and lower respiratory tract infection. None of the 5 patients in Study B2225 with ASM discontinued GLEEVEC due to drug-related adverse events or abnormal laboratory values.

Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The overall safety profile in this HES/CEL small patient population does not seem different from the known safety profile of GLEEVEC observed in other larger populations of hematologic malignancies, such as CML. However, in patients with HES and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of GLEEVEC therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding GLEEVEC (see WARNINGS and PRECAUTIONS). All patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematologic

abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia and anemia.

Dermatofibrosarcoma Protuberans

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with GLEEVEC for DFSP in Trial B2225 are shown in Table 4.

Table 4 Adverse Experiences Regardless of Relationship to Study Drug Reported in DFSP Patients in Trial B2225 (≥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)

Gastrointestinal Stromal Tumors

Unresectable and/or Metastatic Malignant GIST

GLEEVEC was generally well tolerated in patients with unresectable and/or metastatic malignant GIST. Most events were of mild to moderate severity. Drug was discontinued for adverse events in 7 (4.7%) patients in both treatment groups. The most frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue and rash.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with GLEEVEC are shown in Table 5. No major differences were seen in the incidence or severity of adverse events between the 400 mg or 600 mg dose groups.

Table 5 Adverse Experiences Regardless of Relationship to Study Drug Reported in the Unresectable and/or Metastatic Malignant GIST (B2222) trial ($\geq 10\%$) of all patients⁽¹⁾

Preferred Term	All doses	
	(n=147)	
	600 mg n=73	
	All Grades (%)	Grades 3/4 (%)
Blood and lymphatic system disorders		
Anemia	19.7	5.4
Eye disorders		
Lacrimation increased	17.0	0
Gastrointestinal disorders		
Nausea	68.7	4.8
Diarrhea	64.6	4.8
Abdominal pain	57.1	8.8
Vomiting	36.7	4.1
Flatulence	32.0	0
Dyspepsia	15.0	0
Constipation	10.2	0.7
General disorders and administration site conditions		
Any Fluid retention	80.3	9.5
Superficial edema	78.9	5.4
Other fluid retention events ⁽²⁾	13.6	5.4
Fatigue	50.3	1.4
Pyrexia	20.4	1.4
Other hemorrhage	24.5	2.7
Hepatobiliary disorders		
Liver Toxicity	12.2	6.8
Infections and infestations		
Nasopharyngitis	23.8	0
Upper Respiratory Tract Infection	15.6	0
Musculoskeletal. & connective tissue disorders		
Muscle cramps	52.4	0
Musculoskeletal pain	33.3	3.4
Back pain	24.5	0
Join Pain	12.9	0.7
Nervous system disorders		
Headache	36.1	0
Dizziness	11.6	0
Peaces abnormal		
Loose Stools	10.9	0
Psychiatric disorders		
Insomnia	18.4	0.7
Anxiety	8.8	0
Respiratory disorders		
Pharyngolaryngeal Pain	9.5	0
Skin and subcutaneous disorders		
Rash and related terms	45.6	3.4
Surgical and medical procedures		
Operation	10.2	4.8
Vascular disorders		
Any Hemorrhage	29.9	8.2
Upper G-I tract bleeding/perforation	4.1	3.4
Tumor Hemorrhage	2.7	2.7

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

⁽²⁾ Other fluid retention events included pleural effusion and ascites.

Adjuvant Treatment of GIST

The majority of both GLEEVEC and placebo treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST. Drug was discontinued for adverse reactions in 57 patients (17%) and 11 patients (3%) of the GLEEVEC and placebo treated patients respectively. Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distension and diarrhea), fatigue, low hemoglobin and rash were the most frequently reported adverse reactions at the time of discontinuation.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with GLEEVEC are shown in Table 6.

Table 6: Adverse Reactions Regardless of Relationship to Study Drug Reported in the Adjuvant GIST Trial (≥5% of GLEEVEC Treated Patients)

	All CTC Grades		CTC Grade 3 and above	
	GLEEVEC (n=337)	Placebo (n=345)	GLEEVEC (n=337)	Placebo (n=345)
Preferred Term	%	%	%	%
Blood and lymphatic system disorders				
Leukopenia	5.0	2.6	0.3	0
Eye disorders				
Lacrimation Increased	9.8	3.8	0	0
Vision Blurred	5.0	2.3	0	0
Gastrointestinal disorders				
Diarrhea	59.3	29.3	3.0	1.4
Nausea	53.1	27.8	2.4	1.2
Vomiting	25.5	13.9	2.4	0.6
Abdominal Pain	21.1	22.3	3.0	1.4
Dyspepsia	17.2	13.0	0.9	0
Constipation	12.8	17.7	0	0.3
Abdominal Distension	7.4	6.4	0.3	0.3
Flatulence	8.9	9.6	0	0
Abdominal Pain Upper	6.2	6.4	0.3	0
Stomatitis	5.0	1.7	0.6	0
General disorders and administration site conditions				
Fatigue	57.0	40.9	2.1	1.2
Peripheral Edema	26.7	14.8	0.3	0
Facial Edema	6.8	1.2	0.3	0
Hepatobiliary disorders				
Liver enzymes (ALT) Increased	16.6	13.0	2.7	0

Liver Enzymes (AST) Increased	12.2	7.5	2.1	0
Investigations				
Hemoglobin Decreased	46.9	27.0	0.6	0
Weight Increased	16.9	11.6	0.3	0
Neutrophil Count Decreased	16.0	6.1	3.3	0.9
White Blood Cell Count Decreased	14.5	4.3	0.6	0.3
Blood Creatinine Increased	11.6	5.8	0	0.3
Weight Decreased	10.1	5.2	0	0
Blood Alkaline Phosphatase Increased	6.5	7.5	0	0
Platelet Count Decreased	5.0	3.5	0	0
Metabolic and nutritional disorders				
Anorexia	16.9	8.7	0.3	0
Hyperglycemia	9.8	11.3	0.6	1.7
Hypokalemia	7.1	2.0	0.9	0.6
Hypocalcemia	5.6	1.7	0.3	0
Musculoskeletal. & connective tissue disorders				
Muscle spasms	16.3	3.3	0	0
Myalgia	12.2	11.6	0	0.3
Arthralgia	15.1	14.5	0	0.3
Back Pain	7.4	8.1	0.6	0
Pain in Extremity	7.4	7.2	0.3	0
Nervous system disorders				
Headache	19.3	20.3	0.6	0
Dizziness	12.5	10.7	0	0.3
Insomnia	9.8	7.2	0.9	0
Depression	6.8	6.4	0.9	0.6
Dysgeusia	6.5	2.9	0	0
Neuropathy Peripheral	5.9	6.4	0	0
Respiratory disorders				
Cough	11.0	11.3	0	0
Upper Respiratory Tract Infection	5.0	3.5	0	0
Skin and subcutaneous disorders				
Periorbital Edema	47.2	14.5	1.2	0
Rash (Exfoliative)	26.1	12.8	2.7	0
Pruritus	11.0	7.8	0.9	0
Alopecia	9.5	6.7	0	0
Rash	8.9	5.2	0.9	0
Dry skin	6.5	5.2	0	0
¹ All adverse reactions occurring in $\geq 5\%$ of patients are listed regardless of suspected relationship to treatment. A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.				

Adverse Drug Reactions in clinical studies for CML and Unresectable and/or Metastatic Malignant GIST

The following adverse reactions as applicable are ranked under headings of frequency, the most frequent first, using the following convention: *Very common* ($\geq 1/10$); *common* ($\geq 1/100, < 1/10$); *uncommon* ($\geq 1/1000, < 1/100$); *rare* ($\geq 1/10,000, < 1/1000$); *very rare* ($< 1/10,000$), including isolated reports. Adverse reactions reported below are based on the registration studies for CML and GIST. Frequencies are determined by reported related events according to the investigator.

Cardiovascular

Common: flushing¹

Uncommon: palpitations, cardiac failure congestive (on a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML), pulmonary edema, tachycardia, hypertension¹, hematoma¹, hypotension¹, peripheral coldness¹, Raynaud's phenomenon¹

Rare: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion

Clinical laboratory tests (See Tables 7, 8 and 10)

Uncommon: blood CPK increased, blood LDH increased

Rare: blood amylase increased

Dermatologic

Common: pruritus, face edema, dry skin, erythema, alopecia, photosensitivity reaction

Uncommon: rash pustular, sweating increased, urticaria, increased tendency to bruise, exfoliative dermatitis, onychoclasia, folliculitis, petechie, psoriasis, bullous eruption, nail disorder, skin pigmentation changes, purpura, palmar-plantar erythrodysesthesia syndrome

Rare: nail discolouration, vesicular rash, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis (Sweet's syndrome)

Digestive

Common: flatulence, abdominal distension, gastroesophageal reflux, dry mouth, gastritis

Uncommon: stomatitis, mouth ulceration, eructation, malaena, oesophagitis, ascites, gastric ulcer, hematemesis, cheilitis, dysphagia, pancreatitis

Rare: colitis, ileus, inflammatory bowel disease.

General Disorders and Administration Site Conditions

Common: weakness, anasarca, chills, rigors

Uncommon: chest pain, malaise

Hematologic (See Tables 8, 9 and 11)

Common: pancytopenia, febrile neutropenia

Uncommon: thrombocythemia, lymphopenia, eosinophilia, lymphadenopathy
Rare: aplastic anemia, hemolytic anemia

Hepatobiliary disorders

Uncommon: jaundice, hepatitis, hyperbilirubinemia
Rare: hepatic failure, hepatic necrosis (some fatal cases of hepatic necrosis have been reported)

Hypersensitivity

Rare: angioedema

Infections

Uncommon: sepsis, herpes simplex, herpes zoster, sinusitis, cellulitis, influenza, urinary tract infection, gastroenteritis
Rare: fungal infection

Metabolic and nutritional

Common: anorexia, weight decreased
Uncommon: hypophosphatemia, dehydration, gout, appetite disturbances, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia
Rare: hyperkalemia, hypomagnesemia

Musculoskeletal

Common: joint swelling
Uncommon: joint and muscle stiffness
Rare: muscular weakness, arthritis

Nervous system/psychiatric

Common: paresthesia, taste disturbance, hypoesthesia
Uncommon: depression², libido decrease, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor
Rare: increased intracranial pressure, confusion, convulsions, optic neuritis

Neoplasm benign, malignant and unspecified (including cysts and polyps)

Uncommon: Tumor lysis syndrome

Renal

Uncommon: renal pain, renal failure acute, urinary frequency increased, hematuria

Reproductive

Uncommon: erectile dysfunction, breast enlargement, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, scrotal edema

Respiratory

Common: dyspnea, epistaxis, cough
Uncommon: pleural effusion (pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML), pharyngolaryngeal pain, pharyngitis

Rare: pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage

Special senses

Common: eyelid edema, lacrimation increased, conjunctival hemorrhage, conjunctivitis, dry eye, vision blurred

Uncommon: eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema, vertigo, tinnitus, hearing loss

Rare: cataract, papilledema, glaucoma

¹ Vascular disorders (flushing was most common in GIST patients and hematoma was most common in patients with GIST and transformed CML (CML-AP and CML-BC).

² Depression may lead to suicide ideation and/or suicide attempts.

Second malignancies in GLEEVEC- treated patients:

Table 7 Observed and expected numbers of cases of second malignancies (excluding non-melanoma skin cancer) in clinical trials

Cancer type	Person-years	Number of cases Observed	Expected ¹	SIR (95% CI)
Cancer any type	10,967.03	79	91.16	0.87 (0.69-1.08)
Prostate	6,106.54	16	18.70	0.86 (0.49-1.39)
Kidney	10,769.60	3	2.26	1.33 (0.27-3.88)
Urinary bladder	10,766.46	2	3.72	0.54 (0.06-1.94)

¹ Expected in the general population
SIR: Standardized incidence ratio

The numbers of cancers reported in the clinical trials were similar to those expected in the general population. The observed numbers of cases for all cancers, prostate cancer and urinary bladder cancer were slightly lower than those expected in the general population, while the number of observed kidney cancer cases was slightly higher (3 compared to 2.26 expected cases respectively). In all cases, the differences were not statistically significant.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory test abnormalities in CML clinical trials

Cytopenias, and particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at doses ≥ 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease.

In patients with newly diagnosed CML, cytopenias were less frequent than in other CML patients (Tables 8 and 9). The frequency of Grade 3 or 4 neutropenia (ANC $<1.0 \times 10^9/L$) and thrombocytopenia (platelet count $<50 \times 10^9/L$) were higher in blast crisis and accelerated phase (36-48% and 32-33% for neutropenia and thrombocytopenia, respectively, Table 9) as compared to chronic phase CML (27% neutropenia and 21% thrombocytopenia). In chronic phase CML a

Grade 4 neutropenia (ANC $<0.5 \times 10^9/L$) and thrombocytopenia (platelet count $<10 \times 10^9/L$) were observed in 9% and $<1\%$ of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes ranged usually from 2 to 3 weeks and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with GLEEVEC, but can, in rare cases, lead to permanent discontinuation of treatment (see WARNINGS and PRECAUTIONS for Hematologic Toxicity).

Severe elevation of transaminases or bilirubin has been seen in $<5\%$ CML patients and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1.0% of CML patients. There have been cases of hepatic necrosis and cholestatic hepatitis and hepatic failure; in some of which outcome was fatal (See DRUG INTERACTIONS).

Table 8 Newly occurring Grades 3/4 biochemical toxicities in newly diagnosed CML patients

Parameter	GLEEVEC n=551 %		IFN + Ara-C n=533 %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Leucopenia	9.3	0.5	12.9	0.8
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				
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 (AST)/ SGPT (ALT)	4.7	0.5	7.1	0.4

* $p < 0.001$ (Difference in Grade 3 + Grade 4 abnormalities between the two treatment groups).

Table 9 Laboratory test abnormalities in other CML clinical trials

	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	32	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	2.3	0
Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

CTC 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).

Clinically relevant or severe abnormalities of the 12 patients treated with GLEEVEC for DFSP in Trial B2225 are presented in Table 10.

Table 10 Laboratory Abnormalities Reported in DFSP Patients in Trial B2225

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

CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, 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 (Grade 3 $\geq 65-80$ g/L, Grade 4 < 65 g/L), elevated creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN).

In unresectable and/or metastatic malignant GIST patients (study B2222), 6.8% Grade 3 or 4 SGPT (serum glutamic pyruvic transferase) elevations and 4.8% Grade 3 or 4 SGOT (serum glutamic oxaloacetic transferase) elevations were observed. Bilirubin elevation was below 3%.

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values were rare ((Table 11).

Table 11 Laboratory Abnormalities in the Unresectable and/or Metastatic Malignant GIST B2222 Trial

Parameter	All doses (n=147) 400 mg n=73 600 mg n=74 n (%)		
	Baseline †	New or Worsening Highest CTC Grade During Treatment	
CTC Grading	All Grades (1-4)	Grade 3	Grade 4
Hematology parameters			
Anemia	70 (47.6)	8 (5.4)	1 (0.7)
Thrombocytopenia	7 (4.8)	1 (0.7)	0
Neutropenia	10 (6.8)	11 (7.5)	4 (2.7)
Biochemistry parameters			
Elevated creatinine	8 (5.4)	2 (1.4)	0
Reduced albumin	60 (40.8)	5 (3.4)	0
Elevated bilirubin	5 (3.4)	2 (1.4)	2 (1.4)
Elevated alkaline phosphatase	58 (39.5)	2 (1.4)	0
Elevated SGOT (AST)	32 (21.8)	5 (3.4)	2 (1.4)
Elevated SGPT (ALT)	19 (13.0)	9 (6.1)	1 (0.7)

† New or worsening of CTC Grade for any individual patient for whom data is included in the All Grade (1-4) Baseline data cannot be inferred from this table.

CTC grades: neutropenia (grade 1= 1.5-< 2.0 x 10⁹ /L, grade 2=1.0 - < 1.5 x 10⁹ /L, grade 3 =0.5 -< 1.0 x 10⁹/L, grade 4 <0.5 x 10⁹/L), thrombocytopenia (grade 1 < LLN - 75.0 x 10⁹/L, grade 2=50.0 - <75.0 x 10⁹ /L, grade 3=10.0 - <50.0 x 10⁹/L, grade 4 <10.0 x 10⁹/L), anemia (hemoglobin: grade 1 < LLN - 100 g/L, grade 2= 80 - < 100 g/L, grade 3=65 - <80 g/L, grade 4 <65 g/L), elevated creatinine (grade 1 > ULN - 1.5 x ULN, grade 2 > 1.5 - 3.0 x ULN, grade 3 >3.0 - 6.0 x upper limit normal range (ULN), grade 4 >6.0 x ULN), reduced albumin (grade 1 < LLN - 30 g/L, grade 2= 20 - < 30 g/L, grade 3 < 20 g/L, grade 4 -), elevated bilirubin (grade 1 > ULN - 1.5 x ULN, grade 2 > 1.5 - 3 x ULN, grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase (grade 1 > ULN - 2.5 x ULN, grade 2 > 2.5-5 x ULN, grade 3 >5-20 x ULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 1 > ULN - 2.5 x ULN, grade 2 > 2.5 - 5.0 x ULN, grade 3 >5-20 x ULN, grade 4 >20 x ULN).

Adverse Reactions from post-marketing reports

The following types of ADRs have been reported from post-marketing experience and from additional clinical studies with GLEEVEC. They include spontaneous case reports as well as serious ADRs from smaller or ongoing clinical studies and the expanded access programs. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to GLEEVEC exposure.

Cardiovascular: Thrombosis/embolism¹, pericarditis, cardiac tamponade, anaphylactic shock¹
subdural hematoma¹

Dermatology: Lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic syndroms (DRESS), pseudoporphyria

Digestive: Ileus/intestinal obstruction, tumor hemorrhage/tumor necrosis, gastrointestinal perforation (some fatal cases of gastrointestinal perforation have been reported)
Diverticulitis, gastric antral vascular ectasia (GAVE)

General: Motor vehicle accidents

Hepatic: Hepatitis, Hepatotoxicity with fatal outcomes (See **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**)

Infections and Infestations: Hepatitis B virus reactivation

Musculoskeletal: Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain) following long-term treatment observed in CML patients.
Avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy, growth retardation in children

Nervous system/psychiatric: Cerebral edema (including fatalities)

Reproductive: Hemorrhagic corpus luteum / hemorrhagic ovarian cyst

Renal: Chronic renal impairment

Respiratory: Acute respiratory failure (fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions), interstitial lung disease

Special senses: Vitreous hemorrhage

Neoplasm benign, malignant and unspecified (including cysts and polyps):
Tumor lysis syndrome, some of which were fatal.

¹ Vascular disorders.

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs that may alter imatinib plasma concentrations

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

Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (mean C_{max} and AUC of imatinib increased by 26% and 40%, respectively) in healthy subjects when GLEEVEC was co-administered with a single dose of ketoconazole (CYP3A4 inhibitor). Caution is recommended when administering GLEEVEC with inhibitors of the CYP3A4 family (e.g. ketoconazole, erythromycin, clarithromycin, itraconazole, grapefruit juice).

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

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may significantly reduce exposure to GLEEVEC.

Administration of rifampin 600 mg daily for eight days to 14 healthy adult volunteers, followed by a single 400 mg dose of GLEEVEC increased imatinib oral dose clearance by 3.8-fold (90% CI 3.5- to 4.3-fold). Mean C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ decreased by 54%, 68% and 74%, respectively compared to treatment without rifampin.

Similar results were observed in patients with malignant gliomas treated with GLEEVEC while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIADs.

In two published studies, concomitant administration of GLEEVEC and a product containing St. John's wort led to a 30 to 32% reduction in the AUC of GLEEVEC. In patients in whom rifampin or other CYP3A4 inducers are indicated, alternate therapeutic agents with less enzyme induction potential should be considered.

Drugs that may have their plasma concentration altered by GLEEVEC

There is limited data on drug interactions. Since the major metabolic pathway is CYP3A4 mediated and GLEEVEC is an inhibitor of CYP2D6, precaution should be exercised with the co-administration of the following classes of drugs.

Table 12 Common classes of drugs used in patients with CML

CYP3A4			CYP2D6	
Inhibitors	Inducers	Substrates	Inhibitors	Substrates
Cyclosporine Imidazole antifungals Macrolide antibiotics Metronidazole	Antiepileptics Glucocorticoids Rifampicin St. John's wort	Busulphan Calcium-channel blockers Cyclophosphamide Cyclosporine Doxorubicin Epipodophyllotoxins Glucocorticoids Ifosphamide Imidazole antifungals Macrolide antibiotics (Azithromycin, Clarithromycin, Erythromycin) PPIs Retinoic acid Rifampicin Serotonin-H ₃ antagonists Vinca alkaloids	Dextropropoxyphene Doxorubicin Quinidine Vinca alkaloids	Cyclophosphamide Beta blockers Morphine Oxycodone Serotonin-H ₃ antagonists

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. Therefore, caution is recommended when administering GLEEVEC with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimoziide), (See ADVERSE REACTIONS.)

In vitro, GLEEVEC inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23%. Caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with GLEEVEC and metoprolol clinical monitoring should be considered.

In vitro data suggest that GLEEVEC has some capacity to act as an inhibitor of CYP2C9, although at concentrations higher than would be expected in plasma with recommended doses. However, caution should be exercised with the concomitant use of drugs metabolized by CYP2C9 (e.g. warfarin).

In view of the potential interaction between GLEEVEC and warfarin, the international normalised ratio (INR) of patients who require anticoagulation with warfarin should be monitored closely, especially when GLEEVEC dose adjustments are necessary. Consideration should be given to anticoagulation with low-molecular weight heparin or unfractionated heparin.

In vitro, GLEEVEC inhibits acetaminophen O-glucuronidation metabolic pathway with K_i value of 58.5 $\mu\text{mol/L}$. Based on the *in vitro* results, systemic exposure to acetaminophen would be expected to increase when co-administered with GLEEVEC. A clinical study showed that co-administration of GLEEVEC (400 mg/day between days two and eight) in the presence

of single dose acetaminophen (1000 mg/day on day eight) in CML patients did not alter the pharmacokinetics of acetaminophen. GLEEVEC pharmacokinetics was also not altered in the presence of single-dose acetaminophen. However, there are no pharmacokinetic or safety data on the concomitant use of GLEEVEC at doses > 400 mg/day or the chronic use of concomitant acetaminophen and GLEEVEC. Hence CAUTION is recommended in patients on the concomitant use of GLEEVEC with acetaminophen.

Drug-Food Interactions

There were no clinically relevant differences in absorption when GLEEVEC was administered either with food or in the fasting state. The concomitant use of grapefruit juice should be avoided.

Drug-Lifestyle Interactions

Effects on ability to drive and use machines

Reports of motor vehicle accidents have been received in patients receiving GLEEVEC. Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with GLEEVEC. Therefore, caution should be recommended when driving a car or operating machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Therapy should be administered under the supervision of a physician experienced in the treatment of patients with hematological malignancies and/or malignant sarcomas.

The prescribed dose should be administered orally, during a meal and with a large glass of water to minimize the risk of gastrointestinal disturbances. 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 the morning and in the evening. Efficacy data for the 800 mg/day dose are limited.

Dosing in pediatric patients should be on the basis of body surface area (mg/m^2). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. (See CLINICAL TRIALS SECTION AND ACTION AND CLINICAL PHARMACOLOGY SECTION). There is no experience with the use of GLEEVEC in pediatric patients with CML under 2 years of age. There is very limited to no experience with the use of GLEEVEC in pediatric patients in other indications.

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). Traces of the disintegrated tablet left in the glass after drinking should also be consumed.

Treatment should be continued as long as the patient continues to benefit.

For daily dosing of 800 mg, GLEEVEC should be administered using the 400 mg tablet twice a day to reduce exposure to iron.

Preventative measures should be considered prior to treatment with GLEEVEC in patients with increased risk for TLS (see WARNINGS AND PRECAUTIONS and Monitoring and Laboratory Tests).

Recommended Dose and Dosage Adjustment

Chronic myeloid leukemia (CML)

The recommended dosage of GLEEVEC is 400 mg/day for adult patients with newly diagnosed CML or in chronic phase CML. The recommended dosage for adult patients in accelerated phase or blast crisis is 600 mg/day. The recommended dosage of GLEEVEC for pediatric patients with newly diagnosed Ph+ CML is 340 mg/m²/day (rounded to the nearest 100 mg, i.e not to exceed 600 mg).

In CML, a dose increase from 400 mg to 600 mg or to 800 mg/day 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 reactions 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 12 months of treatment; or loss of a previously achieved hematologic and/or cytogenetic response.

Patients with CML should undergo regular response monitoring (See WARNINGS AND PRECAUTIONS). Any changes to patient imatinib therapy (for example, when imatinib dose is lowered due to occurrence of side effects) should be followed by close response monitoring.

Ph+ Acute Lymphoblastic Leukemia (Ph+ALL)

The recommended dose of GLEEVEC for use as a single-agent for induction phase therapy in adult patients with newly diagnosed Ph+ALL, or for adult patients with relapsed or refractory Ph+ ALL is 600 mg/day.

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

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

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

The recommended dose of GLEEVEC is 400 mg/day for adult patients with ASM or SM-AHNMD without the D816V c-Kit mutation or mutational status unknown and not responding satisfactory to other therapies.

For patients with ASM or SM-AHNMD associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR α , a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

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

The recommended dose of GLEEVEC is 100 mg/day for adult patients with HES/CEL.

For HES/CEL patients, a dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. Treatment should be continued as long as the patient continues to benefit.

Dermatofibrosarcoma Protuberans (DFSP)

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

Gastrointestinal stromal tumors (GIST)

Unresectable and/or metastatic malignant GIST

The recommended dose of GLEEVEC is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic malignant GIST, depending on the stage and the progression of the disease. In GIST, a dose increase from 400 mg/day to 600 mg/day or to 800 mg/day for adult patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Adjuvant Treatment of GIST

The recommended dose of GLEEVEC is 400 mg/day for the adjuvant treatment of adult patients at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST. In the clinical study, GLEEVEC was administered for one year. The optimal treatment duration with GLEEVEC is not known.

No dose adjustment of the initial 400 mg a day dose was made in patients with GIST with mild liver function abnormalities.

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

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

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, GLEEVEC should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with GLEEVEC may then be continued at a reduced daily dose (i.e., from 400 mg to 300 mg or from

600 mg to 400 mg, or from 800 mg to 600 mg). In pediatric patients, daily doses can be reduced under the same circumstances from 340 mg/m²/day to 260 mg/m²/day.

Dose Adjustment for Patients with Hepatic Impairment

Patients with mild, and moderate liver dysfunction should be dosed at the minimum effective dose of 400 mg daily and patients with severe liver dysfunction should start at 200 mg daily. In the absence of severe toxicity, a dose increase up to 300 mg daily may be considered. The dose should be reduced if the patient develops unacceptable toxicity (SEE ACTION AND CLINICAL PHARMACOLOGY).

Dose Adjustment for Patients with Renal Impairment

GLEEVEC and its metabolites are not excreted via the kidney to a significant extent. However, it has been shown that exposure to imatinib is increased up to 2-fold in patients with mild (CrCL: 40-59 mL/min) and moderate (CrCL: 20-39 mL/min) renal dysfunction, and that there is a significant correlation in the incidence of serious adverse events with decreased renal function.

In clinical trials to date, the safety and efficacy of GLEEVEC in patients with renal impairment has not been established. Patients with mild or moderate renal dysfunction should be treated with caution, and be given the minimum recommended effective dose of 400 mg daily as starting dose. (SEE ACTION AND CLINICAL PHARMACOLOGY) The dose should be reduced if not tolerable. If tolerated, the dose can be increased for lack of efficacy (See section WARNINGS AND PRECAUTIONS). Treatment of patients with moderate renal insufficiency at 800 mg cannot be recommended as this dose has not been investigated in these patients. The effect of GLEEVEC treatment on patients with severe renal dysfunction (CrCL: <20 mL/min) and on hemodialysis has not been assessed, so treatment of these patients with imatinib cannot be recommended.

Hematologic adverse drug reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia.

ASM or SM-AHNMD associated with eosinophilia and HES/CEL with FIP1L1-PDGFR α fusion kinase (starting dose 100 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 \geq 1.5 x10⁹/L and platelets \geq 75 x10⁹/L. 2. Resume treatment with GLEEVEC at previous dose (i.e. before severe adverse drug reaction).
Chronic phase CML (starting at dose 400 mg) MDS/MPD, ASM/SM-AHNMD, HES/CEL (at 400 mg dose) or GIST (starting dose either 400 mg or 600 mg)	ANC < 1.0 x10 ⁹ /L and/or Platelets < 50 X 10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop GLEEVEC until ANC \geq 1.5 x10⁹/L and platelets \geq 75 x10⁹/L. 2. Resume treatment with GLEEVEC at the original dose of 400 mg or 600 mg (i.e. before severe adverse drug reaction). 3. If recurrence of ANC < 1.0 x10⁹/L and/or Platelets < 50 x10⁹/L, repeat step 1 and resume GLEEVEC at a reduced dose of 300 mg (if starting dose was 400 mg, 400 mg if starting dose was 600 mg).
Newly diagnosed pediatric chronic phase CML (at dose 340 mg/m ² /day)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50 x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop GLEEVEC until ANC \geq 1.5 x10⁹/L and platelets \geq 75 x10⁹/L. 2. Resume treatment with GLEEVEC at previous dose (i.e. before severe adverse drug 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/day.
Accelerated phase CML and blast crisis and Ph+ALL (starting dose 600 mg)	¹ ANC < 0.5 x10 ⁹ /L and/or Platelets < 10 x10 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. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop GLEEVEC until ANC \geq 1 x10⁹/L and platelets \geq 20 x10⁹/L and then resume treatment at 300 mg.
DFSP (at 800 mg dose)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop GLEEVEC until ANC \geq 1.5 x10⁹/L and platelets \geq 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.

ANC: absolute neutrophil count

¹occurring after at least 1 month of treatment

Missed Dose:

If a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.

OVERDOSAGE

Experience with higher than therapeutic doses is limited. Isolated cases of GLEEVEC overdose have been reported spontaneously and in the literature. Generally the reported outcome in these cases was improvement or recovery. In the event of overdose the patient should be observed and appropriate symptomatic treatment should be given.

Events that have been reported at different dose ranges are as follows:

Adult overdose:

1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite, increased bilirubin and liver transaminase level. 1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain. 6,400 mg (single dose): A case report in the literature about one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Pediatric overdose:

One 3 year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhoea and anorexia and another 3 year old male exposed to a single dose of 980 mg dose experienced decreased white blood cell count and diarrhea.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

GLEEVEC (imatinib mesylate) is a protein tyrosine kinase inhibitor, which inhibits the Bcr-Abl tyrosine kinase at the *in vitro*, cellular, and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome-positive chronic myeloid leukemia (CML) and acute lymphoid leukemia (ALL) patients. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of Bcr-Abl positive colonies from CML patients.

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

In addition, imatinib is an inhibitor of several receptor tyrosine kinases: the platelet-derived growth factor receptors (PDGFR- α and PDGFR- β), and the stem cell factor (SCF), receptor (c-Kit), and it inhibits the cellular events mediated by these receptors. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating *kit* mutation.

Constitutive activation of the PDGFR or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of several conditions including MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signaling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

Several mechanisms of resistance have been identified from *in vitro* studies of Bcr-Abl positive cell lines. Mechanisms include amplification of the Bcr-Abl gene and overexpression of the multidrug resistance P-glycoprotein. Mutation or amplification of the Bcr-Abl gene has been described in relapsed patients with advanced stage CML.

Prevalence of Abl kinase domain mutations among samples of resistant CML patients varies across studies, likely reflecting variations in time frames for testing, the duration of imatinib exposure, patient selection differences, and perhaps differences in techniques and sensitivity.

The specific clinical relevance of Abl kinase domain mutations in the prognosis and management of patients with CML requires further study. It is likely that mutations will have different clinical phenotypes, with some being subject to higher-dose imatinib therapy, depending on the IC₅₀ of the mutation, and others requiring alternative treatment strategies.

Recent *in-vitro* experiments have indicated that some mutations remain sensitive to GLEEVEC at high concentrations, other mutants remain unresponsive to dose escalation, which may indicate a kinase-independent, or even Bcr-Abl independent mechanisms of resistance.

Currently identified possible mechanisms of resistance to GLEEVEC can be categorized in two main groups: the mechanisms where Bcr-Abl is reactivated and cell proliferation remains dependent on Bcr-Abl signaling, and mechanisms where the Bcr-Abl protein remains inactivated by GLEEVEC but alternative signalling pathways become activated. Whereas the primary resistance to GLEEVEC seems mostly associated with amplification of the Bcr-Abl gene, secondary resistance (ie. loss of response or progression) appears to be associated with the emergence of mutations of the Bcr-Abl gene (see below):

Currently identified mechanisms of resistance to imatinib

Bcr-Abl dependent mechanisms (cells remain dependent of Bcr-Abl signaling)	Bcr-Abl independent mechanisms (Bcr-Abl is inactivated)
Amplification of Bcr-Abl gene	Activation of signaling pathways downstream of Bcr-Abl
Mutations of Bcr-Abl preventing correct Bcr-Abl imatinib binding	Clonal evolution with appearance of new chromosomal abnormalities
Efflux of imatinib by P-gP associated MDR protein	Activation of leukemogenic pathways unrelated to Bcr-Abl
Protein binding of imatinib (eg. to circulating AGP)	

P-gP: Protein-glyco-Protein
MDR: Multidrug Resistance
AGP: Alpha 1-acid glycoprotein

The clinical utility of detecting mutations remains to be demonstrated, since mutations have been described among GLEEVEC treated patients without evidence of disease progression. In addition, the approach to managing resistance will differ by CML disease stage, irrespective of treatment. Clinical and molecular resistance is much more prevalent among patients with blast crisis and accelerated phase CML, than among patients with chronic phase CML.

Pharmacokinetics

The pharmacokinetics (PK) of GLEEVEC have been evaluated in 591 patients and 33 healthy subjects over a dosage range of 25 to 1000 mg.

Absorption: Mean absolute bioavailability for the capsule formulation is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40-60% after an oral dose. When given with a high fat meal the rate of absorption of imatinib was reduced (11% decrease in C_{max} and prolongation of t_{max} by 1.5 h), with a small reduction in AUC (7.4%) compared to fasting conditions.

Distribution: At clinically relevant concentrations of imatinib, binding to plasma proteins is approximately 95% on the basis of *in vitro* experiments, mostly to albumin and α_1 -acid glycoprotein, with little binding to lipoproteins.

In *in vitro* experiments, the active metabolite, CGP74588, exhibited similar protein binding behaviour to imatinib at clinically relevant concentrations.

Metabolism: 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 and the terminal half-life

is approximately 40 h at steady state. The plasma protein binding of the N-demethylated metabolite CGP74588 was shown to be similar to that of the parent compound in both healthy volunteers and Acute Myeloid Leukemia (AML) patients although there were variabilities in blood distribution and protein binding between AML patients. Some of the AML patients showed a significantly higher unbound fraction of both compounds which led to a higher blood cell uptake.

A phase I study has shown a 4- to 7-fold accumulation of the metabolite CGP74588 at steady state following once daily dosing, which was greater than the parent drug (See below: plasma pharmacokinetics). This might be due to the fact that CGP74588 is metabolized at a 53% lower metabolic conversion rate compared to GLEEVEC in human hepatocytes. The reduced metabolic clearance of CGP74588 is further implied by *in vitro* experiments which showed a lower infinity of CGP74588 to CYP3A4 in comparison to STI571.

Excretion: Based on the recovery of compound(s) after an oral ¹⁴C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Plasma pharmacokinetics: Following oral administration in healthy volunteers, the $t_{1/2}$ was approximately 18 hours suggesting that once daily dosing is appropriate. Plasma pharmacokinetic profiles were analyzed in CML patients on Day 1 and on either Day 7 or 28, by which time plasma concentrations had reached steady state. The increase in mean imatinib AUC with increasing dose was linear and dose proportional in the range 25-1000 mg after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when GLEEVEC is dosed once daily.

The effect of body weight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 l/h, while for a patient weighing 100 kg the clearance will rise to 11.8 l/h. These changes are not considered sufficient to warrant dose adjustment based on body weight. There is no effect of gender on the kinetics of imatinib.

Special Populations and Conditions:

Pediatrics: A total of 31 pediatric patients with either chronic phase CML (n=15), CML in blast crisis (n = 4) or acute leukemias (n=12) have been enrolled in a dose-escalation phase I trial. In this trial the effective dose in pediatric patients was not identified. This was a population of heavily pretreated patients; 45% had received prior BMT and 68% prior multi-agent chemotherapy. Newly diagnosed patients or those eligible for bone marrow transplantation were not studied. The median age was 14 years (range 3 to 20 years). Of the 31 patients, n=12 were three to 11 years old at the start of the study, n= 17 were between 12 and 18 years, and only two were more than 18 years old. Patients were treated with doses of GLEEVEC of 260 mg/m²/day (n=6), 340 mg/m²/day (n=11), 440 mg/m²/day (n= 8) and 570 mg/m²/day (n=6). Dosing based upon body surface area resulted in some patients receiving higher than the adult therapeutic dose, and the effect of this on pediatric patient safety is limited.

As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m²/day achieved similar exposure, respectively, as doses of 400 mg and 600 mg in adult patients, although this

was based upon a small sample size. The comparison of AUC₀₋₂₄ on Day 8 versus Day 1 at the 340 mg/m²/day dose level revealed a 1.7- fold drug accumulation after repeated once daily dosing. As in adults, there was considerable inter-patient variability in the pharmacokinetics, and the coefficient of variation for AUC₀₋₂₄ ranged from 21% (260 mg/m²/day) to 68% (570 mg/m²/day). The AUC did not increase proportionally with dose within the range of doses examined. The active metabolite, GCP 74588, contributed about 20% of the AUC for imatinib. Total plasma clearance is about 8 - 10 L/h at steady state. The plasma AUC of imatinib is significantly lower (*p*=0.02) in children at ages between 2 and <12 years old (29.3 ug*hr/mL) than those at ages between 12 and <20 years old (34.6 ug*hr/mL). However, the difference between the two age groups does not seem to be clinically significant, only 15% of difference (geometric mean of 29.3 in children compared to 34.6 in adolescents). The AUC exposure in both age groups falls within the adult AUC_(0-24h) range, between 24.8 and 39.7 µg*h/ml, achieved at 400 mg and 600 mg daily doses, respectively.

Geriatrics: Based on population PK analysis, there was an effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant.

Hepatic Insufficiency: In a study of patients with mild and moderate hepatic dysfunction (Table 13), the mean exposure to imatinib (dose normalized AUC) did not differ significantly compared with patients with normal liver function. There was a tendency toward an increased exposure in patients with severe liver dysfunction (approximately 45% increase compared with patients with normal liver function). In this study up to 500 mg daily was used in patients with mild liver dysfunction, up to 400 mg daily in patients with moderate, and up to 300 mg daily in patients with severe liver dysfunction.

In the severe liver dysfunction group 29% of patients experienced serious adverse events at the 100 mg dose level, 60% at the 200 mg and 50% of patients treated at the 300 mg dose levels. (See sections WARNINGS and PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Table 13: Liver Dysfunction Classification	
Liver Dysfunction	Liver Dysfunction Tests
Mild	Total bilirubin: = 1.5 ULN SGOT: >ULN (can be normal or <ULN if Total bilirubin is >ULN)
Moderate	Total bilirubin: >1.5-3.0 ULN SGOT: any
Severe	Total bilirubin: >3-10 ULN SGOT: any

ULN=upper limit of normal for the institution

SGOT= serum glutamic oxaloacetic transferase

Renal Insufficiency: Imatinib and its metabolites are not excreted via the kidney to a significant extent.

In a study of patients with varying degrees of renal dysfunction (mild, moderate and severe - see Table 14 below for renal function classification), the mean exposure to imatinib (dose normalized AUC) increased 1.5- to 2-fold compared to patients with normal renal function,

which corresponded to an elevated plasma level of AGP, a protein to which imatinib binds strongly. There was a correlation with the incidence of serious adverse events and decreasing renal function ($p = 0.0096$). In this study, 800 mg daily was used in patients with mild renal dysfunction and 600 mg daily was used in patients with moderate renal dysfunction. The 800 mg dose was not tested in patients with moderate renal dysfunction due to the limited number of patients enrolled. Similarly, only 2 patients with severe renal dysfunction were enrolled at the low (100 mg) dose, and no higher doses were tested. No patients on hemodialysis were enrolled in the study. Since the effect of GLEEVEC treatment on patients with severe renal dysfunction and on hemodialysis has not been sufficiently assessed, treatment of these patients with imatinib cannot be recommended. Patients with mild or moderate renal dysfunction should be treated with caution, and be given the minimum recommended dose of 400 mg daily as starting dose. The dose should be reduced if not tolerable. If tolerated, the dose can be increased for lack of efficacy. Dosing of patients with moderate renal insufficiency at 800 mg cannot be recommended as this has not been investigated (See sections ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Table 14 Renal function classification

Renal dysfunction	Renal function tests
Mild	CrCL = 40-59 mL/min
Moderate	CrCL = 20-39 mL/min
Severe	CrCL = < 20 mL/min

CrCL = Creatinine Clearance

Drug-Drug Interactions

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

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

CYP3A4 Inducers: Administration of rifampin 600 mg daily for eight days to 14 healthy adult volunteers, followed by a single 400 mg dose of GLEEVEC increased imatinib oral dose clearance by 3.8-fold (90% CI 3.5- to 4.3-fold). Mean C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ decreased by 54%, 68% and 74%, respectively compared to treatment without rifampin. In patients in whom rifampin or other CYP3A4 inducers are indicated, alternate therapeutic agents with less enzyme induction potential should be considered (See DRUG INTERACTIONS).

In vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 μ M, respectively. Imatinib is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5 (See DRUG INTERACTIONS).

STORAGE AND STABILITY

Store GLEEVEC at room temperature (15-30°C). Protect tablets from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GLEEVEC (imatinib mesylate) 100 mg tablets

Each tablet contains 100 mg of imatinib (as mesylate beta crystals) and the following inactive ingredients: Cellulose (microcrystalline), crospovidone, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate. The coating contains ferric oxide (red), ferric oxide (yellow), hydroxypropyl methylcellulose, polyethylene glycol, and talc.

GLEEVEC (imatinib mesylate) 400 mg tablets

Each tablet contains 400 mg of imatinib (as mesylate beta crystals) and the following inactive ingredients: Cellulose (microcrystalline), colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, and magnesium stearate. The coating contains ferric oxide (red), ferric oxide (yellow), hydroxypropyl methylcellulose, polyethylene glycol, and talc.

Availability of Dosage Forms

GLEEVEC (imatinib mesylate) 100 mg scored tablets are supplied in cartons containing 6, 12, or 18 blister strips of 10 tablets.

GLEEVEC (imatinib mesylate) 400 mg tablets are supplied in cartons containing 1, 3, or 9 blister strips of 10 tablets.

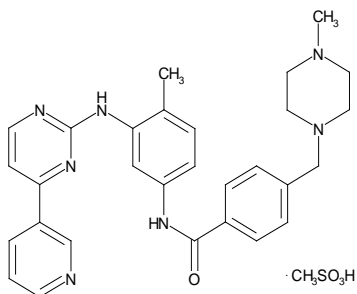
GLEEVEC (imatinib mesylate) 400 mg scored tablets are supplied in cartons containing 1, 3, or 9 blister strips of 10 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name:	Imatinib mesylate
Chemical name:	(4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate)
Molecular formula and	$C_{29}H_{31}N_7O \cdot CH_4SO_3$
Molecular mass:	589.7
Structural formula:	



Physicochemical properties:

Description:	White to off-white to brownish or yellowish tinged powder
Solubility:	Very to freely soluble in water and aqueous solutions at low pH values. The solubility drops in aqueous buffer solution to “insoluble” with an increase of the pH from pH 5.5 to 8.0.
pH:	The pH of a 1% solution in water is approximately 5.5
Melting range:	210-220°C (beta crystal form)
pKa:	7.8, 3.8, and 3.3
Distribution coefficient:	> 100 (n-octanol/phosphate buffer pH 6.8 medium at 37±1°C). Log D = 3.5

CLINICAL TRIALS

Chronic Myeloid Leukemia

Newly diagnosed chronic myeloid leukemia (adults)

An open label, multicenter, international randomized phase III study has been conducted in adult patients with newly diagnosed chronic myeloid leukemia (CML) in which GLEEVEC was compared to a combination of interferon- α plus cytarabine (IFN+Ara-C). Patients showing a lack of response [lack of complete hematologic response (CHR) at six months, increasing white blood cell (WBC) counts or no major cytogenetic response (MCyR) at 24 months], loss of response (loss of CHR or MCyR) or severe intolerance to treatment were allowed to cross over to the alternate treatment arm.

In the GLEEVEC arm, patients were treated 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+Ara-C arm, patients were treated with a target dose of IFN of 5 MU/m²/day subcutaneously. In addition, subcutaneous Ara-C, (20 mg/m²/day), was administered for ten days every month until a complete cytogenetic response (CCyR) had been achieved and confirmed by cytogenetic analysis on two consecutive occasions not more than three months apart. In this trial, at least 80% of patients were brought to baseline conditions by previous treatment with hydroxyurea. Median WBC decreased from 90 x 10⁹/L at diagnosis to 19x10⁹/L. Moreover concurrent administration of hydroxyurea during the first six months of the study was permitted in 44.6% and 74.3% of patients in the GLEEVEC and IFN+Ara-C arms, respectively, to keep the WBC under 20x10⁹/L.

A total of 1106 patients were randomized at 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 to 70 years), with 21.9% of patients 60 years of age or older. There were 59% males and 41% females: 89.9% Caucasian and 4.7% Black patients. At an analysis 7 years after the last patient had been recruited, the median duration of first-line treatment was 82 months and 8 months in the GLEEVEC and IFN + Ara-C arms, respectively, with 60% of patients randomized to GLEEVEC still receiving first-line treatment. Due to discontinuations and crossover, only 2% of those patients randomized to IFN+Ara-C were still on first-line treatment. In the IFN+Ara-C arm withdrawal of consent (13.7%) was the most frequent reason for discontinuation of first-line therapy. Of the patients who crossed over from the control arm (360/553), the reasons for crossover to the GLEEVEC arm were intolerance to treatment (N=145, 40.3%), lack of response (N=97, 27.0%), progression (N=77, 21.4%), and patient refusal to continue on IFN + Ara-C (N=41, 11.4%).

The primary efficacy endpoint of the study was progression-free survival. 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 an increasing WBC despite appropriate therapeutic management in those patients not achieving a CHR. Major cytogenetic response, complete hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis, and survival and quality of life were the main secondary endpoints. Response data are provided in Table 15.

Table 15 Response in newly diagnosed CML study(First Line) (84-month data)

Best response rates	GLEEVEC n=553	IFN + Ara-C n=553
Hematological response¹		
CHR rate n (%) [95% CI]	534 (96.6)* [94.7, 97.9]	313 (56.6)* [52.4, 60.8]
Cytogenetic response²		
Major Cytogenetic response n (%) [95% CI]	472 (85.4)* [82.1, 88.2]	93 (16.8)* [13.8, 20.2]
Unconfirmed ³	490 (88.6)*	129 (23.3)*
Complete Cytogenetic Response n (%) [95% CI]	413 (74.7)* [70.8, 78.3]	36 (6.5) [4.6, 8.9]
Unconfirmed ³	456 (82.5)*	64 (11.6)*
Molecular response⁴		
Major response at 12 months (%)	40	2
Major response at 24 months (%)	54*	NA ⁵

*p<0.001, Fischer's exact test

- ¹ **Hematological response criteria** (all responses to be confirmed after ≥4 weeks): WBC<10x10⁹/L; platelet <450x10⁹/L; myelocyte+metamyelocyte <5% in peripheral blood; no blasts and promyelocytes in peripheral blood; basophils <20%; no extramedullary involvement.
- ² **Cytogenetic response criteria** : complete (0% Ph+metaphases or partial (1-35%).
- ³ Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.
- ⁴ **Major molecular response criteria**: in the peripheral blood, reduction of ≥ 3 logarithms in the amount of Bcr-Abl transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline.
- ⁵ Not Applicable: insufficient data, only two patients available with samples

For analysis of long-term outcomes patients randomized to receive GLEEVEC were compared with patients randomized to receive IFN+ Ara-C. Patients who crossed over prior to progression were not censored at the time of crossover, and events that occurred in these patients following crossover were attributed to the original randomized treatment.

With 7 years of follow-up, there were 93 (16.8%) progression events in the GLEEVEC arm: 37 (6.7%) involving progression to AP/BC, 31 (5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in WBC and 10 (1.8%) CML unrelated deaths. In contrast, there were 165 (29.8%) events in the IFN+Ara-C arm of which 130 occurred during first-line treatment with IFN+Ara-C. These progression events in the IFN + Ara-C arm included 61 (11%) involving progression to AP/BC, 31 (5.6%) loss of MCyR, 46 (8.3%) loss of CHR, 18 (3.3%) increase in WBC, and 5 (0.9%) CML-unrelated deaths.

The estimated rate of progression-free survival at 84 months was 81.2% with [95% CI: 78%, 85%] in the GLEEVEC arm and 60.6% with [95% CI: 56%, 65%] in the IFN+Ara-C arm (p<0.001) (Figure 1).

The estimated rate of patients free of progression to AP or BC at 84 months was significantly higher in the GLEEVEC arm compared to the IFN+Ara-C arm (92.5% with [95% CI: 90, 95] versus 85.1% with [95% CI: 82, 89], (p<0.001 respectively)) (Figure 2).

Figure 1 Time to progression (ITT principle)

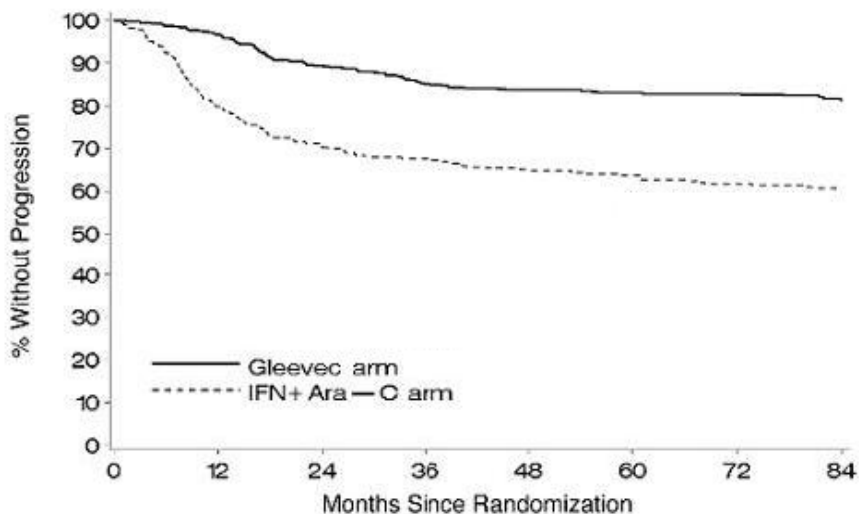
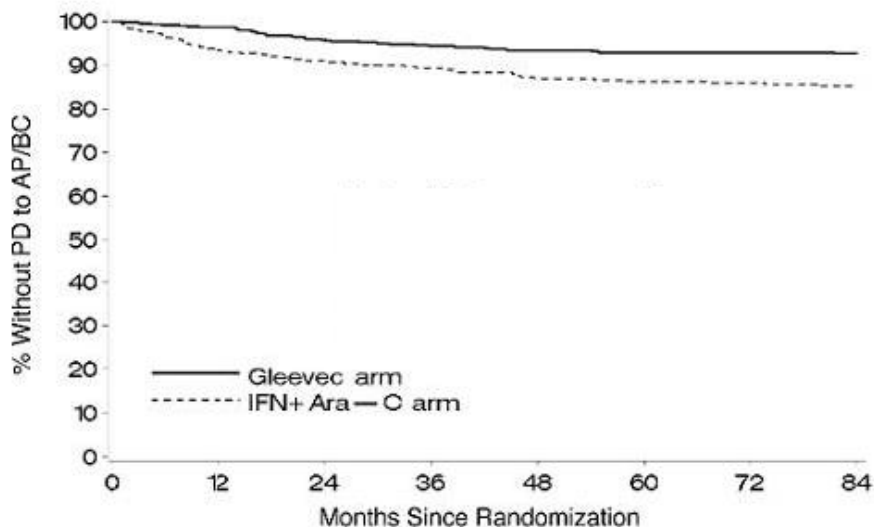


Figure 2 Time to progression to AP or BC (ITT principle)



A total of 71 (12.8%) and 85 (15.4%) patients died in the GLEEVEC and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% [95% CI: 83, 90] vs. 83.3% [95% CI: 80, 87] in the randomized GLEEVEC and IFN+Ara-C groups, respectively ($p=0.073$, log-rank test; $p=0.065$, Wilcoxon test). The probability of remaining progression-free at 60 months was 95% for patients who were in complete cytogenetic response with major molecular response (≥ 3 log reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 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 12 months ($p<0.001$).

In this study, dose escalation were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. After 42 months of follow-up, half of the patients who had increased the dose due to lack of CHR at 3 months, achieved a CHR thereafter. Of the 55 patients who did not have a dose increase 44 patients (80%) also achieved a CHR. Six (50%) of 12 patients with one assessment indicating loss of PCyR or CCyR achieved a MCyR after dose increase and 12 (48%) of the 25 patients without dose increase also achieved a MCyR. Eleven patients who did achieve a complete hematological response at 3 months and a major cytogenetic response at 12 months while on 400 mg daily dose experienced a confirmed (within 4 weeks) loss of their cytogenetic response. Of those, 4 patients did escalate up to 800 mg daily and 2 of them regained a cytogenetic response (1 partial and 1 complete, the latter also achieving a molecular response), while out of 7 patients that did not escalate the dose, only one regained a complete cytogenetic response. The percentage of some adverse events were higher in the 40 patients in whom the dose was increased to 800 mg daily compared to the population of patients before dose increase (n=551). These more frequent adverse events included gastrointestinal hemorrhages, conjunctivitis, elevation of transaminases or bilirubin, hematologic toxicities (mainly anemia and thrombocytopenia) and upper respiratory tract infections. Other adverse events were reported with lower or equal frequency.

Quality of Life (QoL) was measured using the validated FACT-BRM instrument. All domains were assessed and showed that patients in the GLEEVEC arm had significantly higher scores compared to those in the IFN-Ara-C arm. QoL data showed that patients maintain their physical, functional and emotional well-being while on treatment with GLEEVEC.

Pediatric newly diagnosed chronic myeloid leukemia:

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 II trial. Patients were treated with GLEEVEC 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. GLEEVEC treatment induces a rapid response in newly diagnosed pediatric CML patients with a CHR of 80% after 8 weeks of therapy. Those patients for whom cytogenetics was evaluable (46/51) developed a complete cytogenetic response (CCyR) at a rate of 72%. Additionally, partial cytogenetic response (PCyR) was observed in 15% adding up to a Major Cytogenetic response (MCyR) rate of 87%. 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 5.6 months. Fifteen of these patients who achieved CCyR underwent quantitative measurement of BCR-ABL transcript (PCR). Six of these patients (40%) achieved a major molecular response (five of which were complete responses). Patients were allowed to be removed from protocol therapy to undergo alternative therapy including hematopoietic stem cell transplantation as this is the known curative option. Thirty one children received stem cell transplantation. Of the 31 children, 5 were transplanted after disease progression on study and 1 withdrew from study during the first week of treatment and received transplant approximately 4 months after withdrawal. Twenty five children withdrew from protocol therapy to undergo stem cell transplant after receiving a median of 9 twenty-eight day courses (range 4 to 24). Of the 25 patients 13 (52%) had CCyR and 5 (20%) had PCyR at the end of protocol therapy.

Late chronic phase CML and advanced stage CML

Three large, international, open-label, uncontrolled phase II studies were conducted in patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in advanced, blast or accelerated phase disease, in myeloid blast crisis or with CML in the chronic phase in patients who were resistant/refractory to or intolerant of prior interferon-alpha (IFN) therapy. 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, Interferon-failure: 532 patients were treated at a starting dose of 400 mg; The patients were distributed in three main categories according to their response to prior interferon therapy: hematologic failure (29%), cytogenetic failure (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. The primary efficacy variable of the study was the rate of major cytogenetic response (complete plus partial response, 0 to 35% Ph+ metaphases in the bone marrow). 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 16. In this study, 65% of the patients achieved a major cytogenetic response (MCyR), which was confirmed in 59% of patients. Complete cytogenetic response (CCyR) was achieved in 48% of patients, and was confirmed in 38% of patients.

Accelerated phase: 235 patients with accelerated phase disease were enrolled. The first 77 patients were started at 400 mg, the protocol was subsequently amended to allow higher dosing and the remaining 158 patients were started at 600 mg.

The primary efficacy variable was 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. Median duration of treatment was 18 months with 45% of patients treated for ≥ 24 months (maximum = 35 months). A confirmed hematologic response was achieved in 72% of patients (Table 16). Importantly, 27% of patients also achieved a major cytogenetic response, which was confirmed in 21% of patients. Complete cytogenetic response was achieved in 20% of patients, and confirmed in 16%. For the patients treated at 600 mg, the 24-month estimate of the rate of progression-free survival and overall survival is 50% and 66%, respectively. In a multivariate analysis, a dose of 600 mg was associated with an improved time to progression, independent of platelets $\geq 100 \times 10^9/L$, blood blasts $< 15\%$, and hemoglobin ≥ 10 g/L.

Myeloid blast crisis: 260 patients with myeloid blast crisis were enrolled. 165 (63%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis (“pretreated patients”) whereas 95 (37%) had not (“untreated patients”). The first 37 patients were started at 400 mg, the protocol was subsequently amended to allow higher dosing and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the 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. Median duration of treatment was 4 months with 21% of patients treated for ≥ 12 months and 10% for ≥ 24 months (maximum = 35 months). In this study, 31% of patients achieved a hematologic response (36% in previously untreated patients and 22% in previously treated patients).

Table 16 Response in other CML clinical studies

	Chronic phase IFN failure 400mg (n=532)	Accelerated phase 600 mg n=158 400 mg n=77	Myeloid blast crisis 600 mg n=223 400 mg n=37
% of patients (CI 95%)			
Hematologic response¹	95% (92.3,96.3)	72% (65.3, 69.2)	31% (25.2, 36.8)
Complete hematologic response (CHR)	95%	42%	8%
No evidence of leukemia (NEL)	Not applicable	12%	5%
Return to chronic phase (RTC)	Not applicable	17%	18%
Major cytogenetic response²			
Unconfirmed	65% (60.2, 68.5)	27% (21.7, 33.4)	15% (11.2, 20.4)
Confirmed	59% (54.9, 63.4)	21% (16.2, 27.1)	7% (4.5, 11.2)
Complete Cytogenetic response³			
Unconfirmed	48%	20%	7%
Confirmed	38%	16%	2%

¹Hematologic 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

²Cytogenetic response criteria: A major response combines both complete and partial responses: complete (0% Ph+ metaphases), partial (1%-35%).

³Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

The median time to hematologic response was 1 month.

In late chronic phase CML, with a median time from diagnosis of 32 months, an estimated 87.8% of patients who achieved MCyR maintain their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [88.3, 93.2].

In accelerated phase, median duration of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5 months for 400 mg, $p=0.0035$). An estimated 63.8% of patients who achieved MCyR were still in response 2 years after achieving initial response. The median survival was 20.9 [13.1, 34.4] months for the 400 mg group and was not yet reached for the 600 mg group ($p=0.0097$). An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2 years of treatment in the 400 mg vs. 600 mg dose groups, respectively ($p=0.0088$).

In blast crisis, the estimated median duration of hematologic response is 10 months. An estimated 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after achieving their initial response. Median survival was 6.9 [5.8, 8.6] months and an estimated 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

Acute Lymphoblastic Leukemia

Newly diagnosed Ph+ ALL:

GLEEVEC, when used as a single agent in an induction phase in a controlled trial of 55 newly diagnosed patients aged 55 years and over (ADE10) resulted in a significantly higher rate of complete hematological remission when compared to chemotherapy induction (96.3% vs. 50%; $p=0.0001$).

Table 17 Effect of GLEEVEC in newly diagnosed Ph+ ALL patients (600 mg/day)

Study	ADE10 [§] (Controlled study)	
	GLEEVEC induction	CHT induction
N (evaluable for CHR)	27	26
CHR (%)	96	50*
95% C.I.	81 - 100	30 - 70
N (overall)	28	27
1-year DFS (%)	54	
1-year OS (%)	54	
CHR = complete haematological response CHT = chemotherapy * $p<0.01$ § after induction (Complete remission was achieved as a result of induction treatment in both arms).		

Relapsed or refractory Ph+ ALL:

In study 0109, a total of 43 patients with relapsed or refractory Ph+ALL received the initial dose of 600 mg and 3 patients with relapsed or refractory Ph+ALL received the initial dose 400 mg.

The results in 3 patients with relapsed or refractory Ph+ALL showed that the initial dose of 400 mg/day was insufficient for achieving hematological responses.

Table 18 Effect of GLEEVEC on relapsed or refractory Ph+ALL (600 mg/day)

	Phase II Study No. 0109 (N=46) ¹ N(%)
Confirmed Hematologic Response	12 (26.1)
CHR	4 (8.7)
NEL	1(2.2)
RTC	7 (15.2)
Confirmed Cytogenetic Responses	
MCyR	12 (26.1)
CCyR	7 (15.2)
PCyR	5 (10.9)

¹43/46 patients were relapsed or refractory Ph+ALL

NEL= No Evidence of Leukemia

CHR = Complete Hematological Response

RTC= Return to Chronic Phase

The median time to hematologic response was 1 month.

The median duration of hematologic response was 3.42 months

The median time to progression in patients started with 600 mg was 2.56 months

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

One open label, multicentre, phase II clinical trial (Study B2225) was conducted testing GLEEVEC in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. 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 hematologic response and 9 (29%) a complete cytogenetic response (39% including major and partial responses). Of note, the malignancy carried a translocation, usually involving the chromosome t5q33 or t4q12, resulting in a PDGFR gene re-arrangement in 14 evaluable patients. All of these patients achieved a hematologic response (12 completely). Cytogenetic response was evaluated in 11 out of 14 patients, all of whom responded (9 patients completely). Only 2 (13%) out of the 16 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematologic response and one (6%) 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 to 26.7) in the 7 patients treated within Study B2225 and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 19.

Table 19 Response in MDS/MPD

	N	Complete hematologic response	Cytogenetic response
	(Number of patients)	(%)	(%)
Overall population	31	14 (45)	12 (39)
Chromosome t5 involved	12	12 (100)	10 (83)
Chromosome t4 involved	2	2 (100)	1 (50)
Others / no translocation	16	2 (13)	1 (6)
Molecular relapse	1	NE	NE

NE: Not evaluable

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

One open-label, multicentre, phase II clinical trial (Study B2225) was conducted testing GLEEVEC in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic mastocytosis (ASM). The ASM patients were treated with GLEEVEC 100 mg to 400 mg daily. The ages of these 5 patients ranged from 49 to 74 years. A further 25 patients with ASM aged 26 to 85 years were reported in 10 published case reports and case series. These patients also received GLEEVEC at doses of 100 mg to 400 mg daily. Of the total population of 30 patients treated for SM, 10 (33%) achieved a complete hematologic response and 9 (30%) a partial hematologic response (63% overall response rate).

Cytogenetic abnormalities were evaluated in 21 of the 30 ASM patients treated GLEEVEC from the published reports and Study B2225. Eight out of these 21 patients had FIP1L1-PDGFR α fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I). Sixteen patients had unknown or no detectable cytogenetic abnormality and 50% achieved hematologic responses (7 partial and 1 complete) with GLEEVEC. Four patients showed a D816V c-Kit mutation and one with concomitant CML and SM achieved a complete hematologic response with GLEEVEC. The majority of ASM patients reported in the reviewed published medical literature with the D816V c-Kit mutation are not considered sensitive to GLEEVEC. Median duration of GLEEVEC therapy for the 5 ASM patients in Study 2225 was 13 months (range 1.4-22.3 months) and ranged between 1 month and more than 30 months in the responding patients reported in the published medical literature. A summary of the response rates to GLEEVEC in ASM is provided in Table 20.

Table 20 Response in ASM

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFR α fusion kinase (or CHIC2 deletion)	8	8 (100%)	0 (0%)
Juxtamembrane mutation	2	0 (0%)	2 (100%)
Unknown or no cytogenetic abnormality detected	16	1(6%)	7(44%)
D816V mutation	4	1*(25%)	0 (0%)
Overall totals	30	10 (33%)	9 (30%)

*Patient had concomitant CML and ASM

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

One open-label, multicentre, phase II clinical trial (Study B2225) was conducted testing GLEEVEC in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. In this study, 14 patients with HES/CEL were treated with 100 mg to 1000 mg of GLEEVEC daily (the recommended dose for this indication is 100 mg/day to 400 mg/day). The ages of these patients ranged from 16 to 64 years. A further 170 patients with HES/CEL aged 11 to 78 years were reported in 42 published case reports and case series. These patients received GLEEVEC at doses of 75 mg to 800 mg daily. Results are provided in Table 21.

Table 20 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
Positive FIP1L1-PDGFR α fusion kinase	69	69 (100%)	0 (0%)
Negative FIP1L1-PDGFR α fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Overall totals	184	115 (62%)	16 (9%)

Dermatofibrosarcoma Protuberans (DFSP)

One open label, multicentre, phase II clinical trial (Study B2225) was conducted testing GLEEVEC in a diverse population of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with GLEEVEC 800 mg daily. The primary efficacy endpoint was an objective response rate. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial resective surgery and not considered amenable to further resective surgery at the time of study entry.

The median duration of therapy in Study B2225 was 6.2 months, with a maximum duration of 24.3 months. In Study B2225, one of the 12 DFSP patients achieved a complete response (8%) and 8 patients (66%) achieved partial response, 3 of which were rendered disease free by surgery. Responses to treatment are described in Table 22.

Table 22 Response in DFSP

Tumor response	Number of patients (N=12) (Study B2225)	%
Complete response	1	8
Partial response[®]	8 (5+3)	66
Total	9	75

[®] 5 patients made disease free by surgery

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 adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) GLEEVEC daily. The pediatric patient received 400 mg/m²/daily, subsequently increased to 520 mg/m²/daily. The approved pediatric dose in CML is 340 mg/m²/day (rounded to the nearest 100 mg, i.e not to exceed 600 mg). In the published literature duration of therapy ranged between 4 weeks and more than 20 months. Three (50%) of the 6 patients achieved a complete response and 2 (33%) achieved partial response, with one of the partial responders then rendered disease free by surgery.

Unresectable and/or Metastatic Malignant Gastrointestinal Stromal Tumors

One phase 2, open-label, randomized multinational study (B2222) was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. These patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit -positive malignant GIST that was unresectable and/or metastatic. 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 evidence of efficacy was based on objective response rates. Tumors were required to be measurable in at least one site of disease, and response characterization based on Southwestern Oncology Group (SWOG) criteria. Results are provided in Table 23.

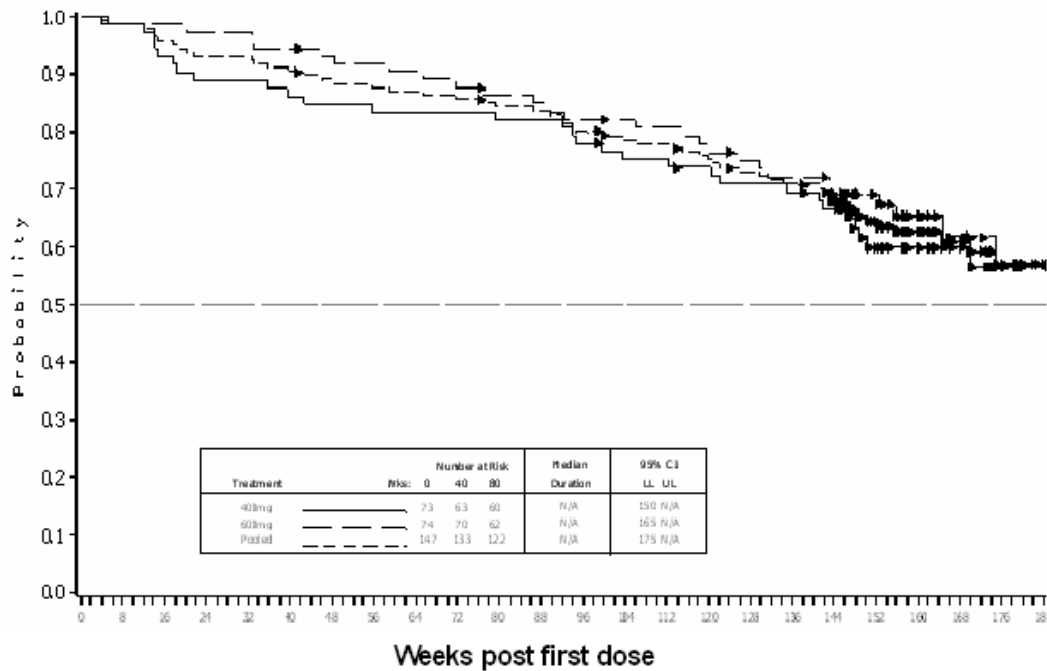
Table 23 Best Tumor Response in Trial STIB2222 (GIST)

	All doses (n=147) 400 mg n= 73 600 mg n=74 n (%)
Best response	
Complete response	1(0.7)
Partial response	98 (66.7)
Stable disease	23 (15.6)
Progressive disease	18 (12.2)
Not evaluable	5 (3.4)
Unknown	2 (1.4)

There were no differences in response rates between the two dose groups. A significant number of patients who had stable disease at the time of the interim analysis did achieve a partial response with longer treatment (median follow-up 31 months). Median time to response was 13 weeks (95% CI 12 to 23). Median time to treatment failure in responders is 122 weeks (95% CI 106 to 147), while in the overall population is 84 weeks (95% CI 71 to 109). The median overall survival has not been reached. The Kaplan-Meier estimate for survival after 36-months follow-up is 68% (Figure 3).

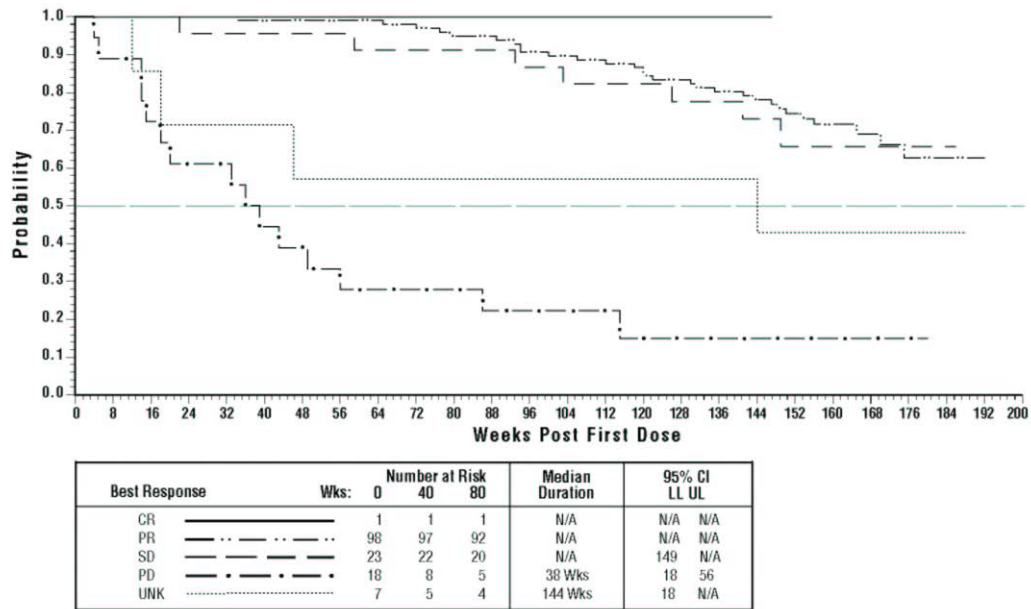
Figure 3: Kaplan-Meier estimate for survival after 36-months

Kaplan-Meier estimate of overall survival since start of study by treatment



Hazard ratio: 0.852, Log rank test p=0.5537.

Figure 4: Kaplan-Meier estimate of overall survival since start of study by best response.



Two randomized studies were conducted comparing GLEEVEC 400 mg versus 800 mg/day as a starting dose: Intergroup Study S0033 and a European-Australian phase III trial (EORTC). Study S0033 showed no significant differences in efficacy between a starting dose of 400 mg and a starting dose of 800 mg daily. The EORTC trial also did not show significant differences in terms of response or overall survival. However, the EORTC trial reported a statistically significant advantage in progression-free survival with the higher dose of GLEEVEC. Grade 3 to 5 toxicities were described more often in high-dose patients in both studies.

The clinical benefit of dose escalation to 800 mg after progression is uncertain. In three randomized clinical trials (B2222, S0033 and EORTC) the daily dose of GLEEVEC was escalated to 800 mg in patients progressing at the lower daily dose of 400 mg. A total of 257 escalated their dose to 800 mg daily; 8 patients achieved a partial response and 71 patients a stabilization of their disease after dose escalation. The dose escalation in the EORTC study led to a significant increase in anemia and fatigue, although fewer cases of neutropenia were reported after the dose escalation to 800 mg.

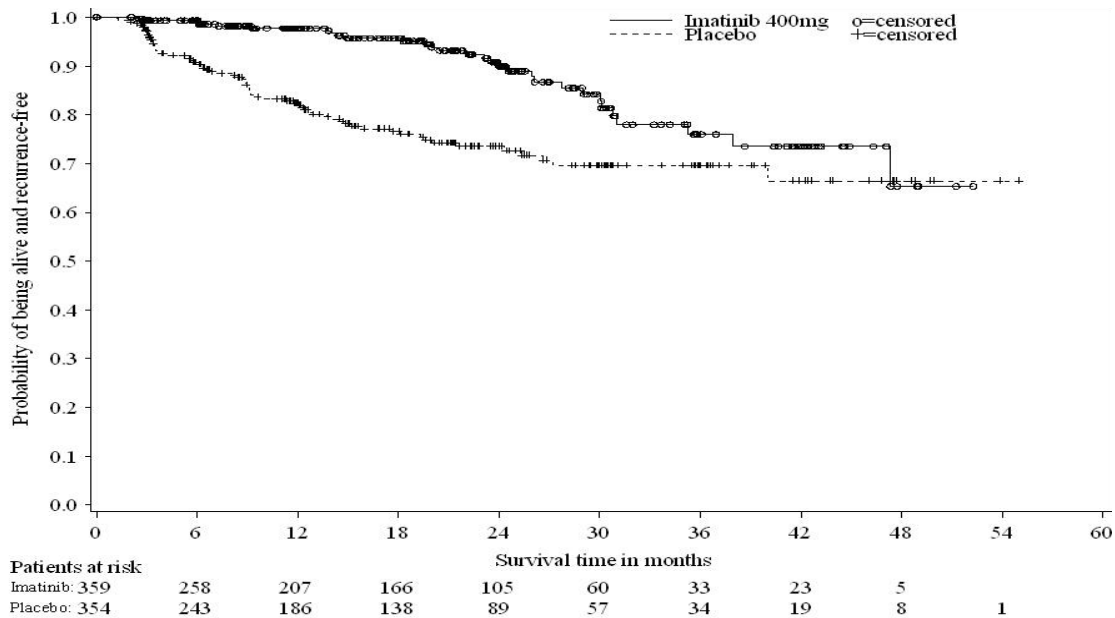
Adjuvant Treatment of GIST

In the adjuvant setting, GLEEVEC was investigated in a multicentre, double-blind, placebo-controlled, randomized phase III study (Z9001) involving 713 patients. The ages of these patients ranged from 18 to 91 years. Patients who were included had a histologic diagnosis of primary GIST expressing KIT protein by immunochemistry and a tumor size ≥ 3 cm in maximum dimension, with complete gross resection of primary GIST within 14 to 70 days prior to registration. After complete gross resection of primary GIST, patients were randomized to one of the two arms: GLEEVEC at 400 mg/day or matching placebo for one year.

The primary efficacy endpoint of the study was recurrence free survival (RFS) defined as the time from date of randomization to the date of recurrence or death from any cause. At a median follow up of 14.0 months, there had been 30 RFS events in the GLEEVEC arm and 70 RFS events in the placebo arm (hazard ratio 0.398 [95%CI: 0.259 to 0.610], two-sided log-rank

$p < 0.0001$). Based on an interim analysis, the trial was stopped early and placebo patients were allowed to cross over to GLEEVEC. Overall survival data are immature due to short follow up time

Figure 5 Recurrences Free Survival



Risk of recurrence was also retrospectively assessed in this trial based on the prognostic factors of tumour size, mitotic index, and tumour location. Mitotic index data were available for 556 of 713 patients in the ITT population. The results of subgroup analyses using the United States National Institutes of Health (NIH) and the Armed Forces Institute of Pathology (AFIP) risk classifications demonstrate benefit from use of adjuvant GLEEVEC in the moderate and high risk groups, but not in the low and very low risk groups. See Table 24:

Table 24 Summary of Z9001 trial RFS analyses by NIH and AFIP risk classifications

RISK CRITERIA	Risk Level	% of pts	#events / #pts	Overall HR (95%CI) [‡]	RFS Rates (%)	
					12 month	24 month
					GLEEVEC vs. Placebo	GLEEVEC vs. Placebo
NIH	Low	29.5	0/86 vs 2/90	N.E.	100 vs 98.7	100 vs 95.5
	Intermediate	25.7	4/75 vs 6/78	0.59 (0.17, 2.10)	100 vs 94.8	97.8 vs 89.5
	High	44.8	21/140 vs 51/127	0.29 (0.18, 0.49)	94.8 vs 64.0	80.7 vs 46.6
AFIP	Very Low	20.7	0/52 vs 2/63	N.E.	100 vs 98.1	100 vs 93.0
	Low	25.0	2/70 vs 0/69	N.E.	100 vs 100	97.8 vs 100
	Moderate	24.6	2/70 vs 11/67	0.16 (0.03, 0.70)	97.9 vs 90.8	97.9 vs 73.3
	High	29.7	16/84 vs 39/81	0.27 (0.15, 0.48)	98.7 vs 56.1	79.9 vs 41.5

[‡]Full follow-up period

N.E = Non Estimate

TOXICOLOGY

Acute Toxicity

Species	Route	Doses (mg/kg)	Main findings
Rat	i.v.	10,30 &100	1 death at 100 mg/kg attributed to lung injury, due to precipitation of the compound. Well tolerated at 10 and 30 mg/kg.

Doses higher than 100 mg/kg were not administered due to the limited solubility of imatinib at neutral pH. The compound was well tolerated at both the low and mid dose. However, there was one death at the high dose (out of ten rats treated) which occurred 30 minutes post-dose. Death was attributed to lung injury, most probably as a result of precipitation of the compound in the pulmonary microcirculation. No other treatment-related changes were noted. Based on these results, 30 mg/kg is considered to be the maximum dose of STI571 which can be administered by slow i.v. bolus injection to rats without causing symptoms.

Subacute and Chronic Toxicity

Study Type	Species	Route	Doses (mg/kg)	Findings
Intravenous				
2 weeks	Rat	i.v.	0.3, 3 & 30	At ≥ 0.3 mg/kg, decreased WBC/lymphocytes. At 30 mg/kg, slight reduction in erythrocyte parameters and thymic atrophy. Slight inflammation at injection sites at all dosages. NOAEL 3 mg/kg.
4 weeks	Rat	i.v.	0.1, 3 & 30	No major findings; increased prostate weight without microscopic changes at ≥ 3 mg/kg.
rising dose	Dog	i.v.	3, 10 & 30	At 30 mg/kg, decreased WBC & absolute neutrophil counts, increased ALT. Clinical signs included hypoactivity and hypersensitivity to touch.
4 weeks	Dog	i.v.	3, 10 & 30	At 10 mg/kg, changes confined to decreased WBC & neutrophil counts. At 30 mg/kg, local reaction at injection sites, ataxia, hypoactivity, skin changes, decreased erythrocyte parameters, WBC & neutrophils, increased ALT, perivascular fibrosis & necrosis, thrombosis and edema at the injection site, decreased testis weight without microscopic change.
4 weeks	Dog	i.v.	20 & 60: 3 hour infusion/day for 7 days; 24 hour infusion thereafter	Mortality at 60 mg/kg. At ≥ 6 mg/kg, increased granulopoiesis decreased RBC parameters. At ≥ 20 mg/kg, decreased WBC, biochemical changes in serum indicating liver toxicity, necrotizing phlebitis, thrombosis in various organs; fatty replacement of bone marrow cells. At 60 mg/kg, reduced erythropoiesis. No NOAEL.
Intraperitoneal				
2-weeks	Rat	i.p.	0.3, 3 & 30	At 30 mg/kg, decreased erythrocyte parameters and alkaline phosphatase levels. Inflammation of the parietal and visceral peritoneum. NOEL 3 mg/kg, with the exception of mild effects at the injection site.
Oral				
2 weeks	Rat	p.o.	60, 200 & 600	Death or early kill at 600 mg/kg, with general deterioration. At all doses, evidence in serum of dose-related liver effects, hemorrhagic ovaries, increased mitoses in the liver; red cell, WBC/lymphocyte counts reduced, hypocellularity of bone marrow. At ≥ 200 mg/kg, enlarged stomachs & degenerative changes, including vacuolation, single cell necrosis or more widespread necrosis in a number of tissues, predominantly of epithelial origin; histiocytosis. At 600 mg/kg, hypertrophy of Kupffer cells, accumulation of macrophages in blood vessels in liver and lung, atrophic changes in thyroid, salivary, Harderian and mammary glands, prostate and seminal vesicles. Atrophy and histiocytosis in lymphoid tissues. All effects dose- related.
13 weeks	Rat	p.o.	6, 20 & 60	At 60 mg/kg, evidence of liver effects in serum. At 20 and 60 mg/kg, decreases in RBC parameters & decreased cellularity of bone marrow. Hyperplasia of transitional epithelium in renal papilla & bladder at all dosages, minimal at 6 mg/kg. Lymphoid & plasma cell hyperplasia in lymph nodes at ≥ 20 mg/kg. At 60 mg/kg, increased mitotic figures in the liver, hemorrhagic ovaries, vacuolation of Harderian glands, increased alveolar macrophages; hemorrhage, hemosiderosis and increased histiocytes in mesenteric lymph nodes. Effects at 6 mg/kg confined to microscopic findings in kidney/bladder.
13 weeks (repeated)	Rat	p.o.	0.3, 1, 3 & 10	No effect at any dose level.

26-week	Rat	p.o.	5, 15, 50	<p>50 mg/kg: Mortality (2m). Red ears, squinting, swollen appendages, red feet, dry perineal staining, apparent blood or dark yellow urine on cage paper, swollen muzzles and appendages, and dry staining of fur. Slight decrease in body weight (f). Decreased neutrophils, eosinophils, hematocrit, hemoglobin, platelets; increased MCV, MCH, MCHC and red cell distribution width. Increased AST, ALT, total protein, albumin, globulin; decreased A/G ratio, sodium, cholesterol and triglycerides. Increased heart (f), adrenal, liver (m), thyroid (m) and ovary weights; decreased pituitary (f) and testis weights. Enlarged masseter muscles and dark or red ovarian nodules. Hemorrhagic and/or cystic corpora lutea, hemosiderin-laden macrophages in ovaries, foamy macrophage accumulation in lungs, focal angiectasis of adrenal cortex, hypertrophy of masseter muscles, focal mineralization/hyperplasia of renal pelvic epithelium and focal new bone formation.</p> <p>≥ 15 mg/kg: Prominent eyes, wet perineal staining, increased incidence/frequency of chromodacryorrhea and red penile discharge. Decreased RBC counts and platelets. Increased heart (m) and spleen weights. Focal fibrosis of bone marrow, atrophy of acinar cells of harderian gland, increased eosinophilic macrophages in mesenteric lymph nodes.</p> <p>≥ 5 mg/kg: Salivation, presence of oral red substance, chromodacryorrhea, increased incidence/frequency of chromorhinorrhea.</p> <p>Most changes were reversible or partially reversible by the end of the recovery period. NTEL = 5 mg/kg.</p>
2-week	Dog	p.o.	10, 30 & 100	<p>No deaths. Occasional emesis and diarrhea at 100 mg/kg. Evidence in serum of liver changes, and decreased leucocyte counts & RBC parameters at 30 & 100 mg/kg. At 100 mg/kg, liver weight increased & centrilobular/ midzonal hepatocyte hypertrophy with increased mitosis and apoptosis, vacuolar degeneration hyperplasia/hypertrophy of epithelium of intrahepatic bile ducts and gall bladder. Vacuolar degeneration of gastric mucosa and renal pelvis. Fibrin thrombi in capillaries of small intestine villi with vasculitis and edema. Decreased thymus weight, lymphocytolysis in lymphoid organs, and bone marrow hypocellularity (dose related) at ≥ 30 mg/kg. NOEL 10 mg/kg.</p>
13 weeks	Dog	p.o.	3, 10, 30 & 100 reduced to 50	<p>Death in 1 male at 100 reduced to 50 mg/kg. At ≥ 10 mg/kg, dose-related diarrhea; decreases in RBC counts, and bone marrow hypo-cellularity in some animals; increased ovary weights, hepatic inflammation; gastric & small intestinal changes; thyroid weights decreased with follicular atrophy; increased splenic hemopoiesis. At >30 mg/kg dose-related emesis; decreased WBC, liver toxicity markers in serum; bile duct hyperplasia; pigment deposition in various tissues; thymic atrophy; focal acinar atrophy in the pancreas; reduced spermatogenesis. At high dose decreased testis weight, vacuolation of hepatocytes & bile duct epithelium; cystic corpora lutea containing hemorrhagic fluid; after recovery period peri-biliary fibrosis also present. NOEL = 3 mg/kg.</p>
4 weeks (exploratory)	Dog	p.o.	100	<p>Morbidity (1m). Salivation and vomiting, resistance to dosing, headshaking, diarrhea, hypoactivity, grey discoloration of fur. Moderate to marked decreased food consumption and body weight loss (reversible). Slight to moderate anemia (decreased reticulocytes and moderately decreased WBC due to decreased neutrophils). Liver alterations: degenerative lesions in biliary system (reversible) and hepatocytes (non-reversible), inflammatory cell infiltration, pigment deposition (mainly Kupffer cells) and bile duct hyperplasia, peribiliary fibrosis and increased perivascular infiltration of granulocytes and precursor cells. Electron microscopy: myeloid bodies in hepatocytes and Kupffer cells. Immunohistochemical analysis: antibodies reacting with nucleoli of hepatocytes and presence of bile duct epithelial cells.</p>
2 weeks	Monkey	p.o.	10, 30, 100 & 300 reduced to 200	<p>Single doses of 200 and 300 mg/kg not tolerated. At 100 mg/kg emesis, decreased body weight, slight decrease in hematocrit, centrilobular vacuolation of the liver. NOEL = 30 mg/kg</p>

13 weeks	Monkey	p.o.	3, 15 & 75	Reduced erythrocyte parameters, emesis, pale gums and skin at 75 mg/kg/day. One female at 15 mg/kg/day also showed pale gums and skin. No test-article-related macroscopic or microscopic changes. NTEL = 15 mg/kg/day.
2-week b.i.d.	Monkey	p.o.	20, 75 & 150→100	Twice daily dosing. Unscheduled sacrifice 150→100 due to poor general condition. Clinical signs at doses ≥75mg/kg: diarrhea, fecal changes, pale gums, and emesis with or without feed. At 150→100 increased creatinine, BUN, total bilirubin and decreased chloride and sodium; focal mineralization and dilatation of kidney tubules; tubular nephrosis; vacuolization of centrilobular hepatocytes; thymic atrophy. Toxicokinetics: No apparent gender difference in exposure, proportional increase in plasma concentrations seen with increasing dose. AUC ₍₀₋₁₈₎ : 1160, 40700 and 34550 ng·h/ml (m), 3270, 9430 and 41250 ng·h/mL (f).
39-week b.i.d.	Monkey	p.o.	15, 30, 80	Results at 6 months: Twice daily dosing 80 mg/kg: Reduced feces, diarrhea (m, f), and reddened conjunctiva/eyelid, pale gingiva (m). Decreased food consumption and body weight change (f). ≥ 30 mg/kg: Decreased food consumption and body weight change (m). Reduced albumin. Decreased RBC count, hemoglobin and hematocrit, increased MCV, MCH and MCHC. Presence of Plasmodium species (malaria). ≥ 15 mg/kg: Soft feces.

The toxicity after i.v. bolus administration was qualitatively similar to that seen after oral dosing. Irritation at the injection site was seen after peripheral i.v. administration in most studies using this route of administration.

Mild to moderate hematological changes were observed in rats, dogs and monkeys at oral doses ≥ 20 , 10 and 75 mg/kg, respectively. Red blood cells were generally affected at doses slightly lower than those causing a decrease of white blood cell formation. Bone marrow changes reflected the effects on peripheral blood in rats and dogs. Atrophy of lymphoid organs, lymphocytolysis and/or lymphoid depletion were observed at oral doses ≥ 200 mg/kg in the rat and ≥ 30 mg/kg in the dog. A slight to moderate reduction in spermatogenesis was observed in the dog ≥ 30 mg/kg and in the rat fertility study at a dose of 60 mg/kg. Enlarged corpora lutea with hemorrhagic fluid were observed in rats at doses ≥ 60 mg/kg and in dogs at 100→50 mg/kg/day. Diarrhea was observed in the dog at oral doses ≥ 3 mg/kg/day. Emesis was observed at oral doses of ≥ 30 mg/kg in the dog and ≥ 75 mg/kg in the monkey. Atrophy of the intestinal mucosa, vacuolar degeneration of the gastrointestinal epithelium and single cell necrosis were observed at doses ≥ 10 mg/kg in the dog and at 600 mg/kg in the rat. The effects on bone marrow, lymphoid tissues, testis/ovaries, and gastrointestinal (GI) tract can be explained by an exaggerated pharmacological effect of imatinib on its different molecular targets.

The kidney was a target organ in rats and monkeys. In rats, hyperplasia of the transitional epithelium in the renal papilla and in the urinary bladder was observed at doses ≥ 6 mg/kg without changes in serum or urinary parameters. These findings may reflect local irritation of the compound to the urinary tract, since it has shown to be a local moderate irritant after i.v. administration. In monkeys, focal mineralisation and dilatation of renal tubules, and tubular nephrosis was seen in a 2-week oral dose range finding study at 150→100 mg/kg. Biochemical changes indicating renal dysfunction (increased BUN and creatinine, electrolyte changes) were noted.

The liver was a target organ in rats and dogs. Increases in transaminases, and decreases in cholesterol, triglycerides, total protein and albumin were observed in both species. Liver toxicity was greater in dogs, as reflected by more extensive microscopic findings consisting of mild multifocal hepatocellular necrosis (single cell type) and single cell necrosis in bile ducts with reactive hyperplasia, and/or inflammation adjacent to blood vessels and bile ducts at doses ≥ 10 mg/kg, most pronounced at the 100/50 mg/kg/day. After the recovery period, liver lesions were more severe than in the main study, associated with peribiliary fibrosis and increased incidence and severity of bile duct hyperplasia. Antinucleolar antibodies located in hepatocytes and in epithelial bile duct cells were detected in the 4-week dog exploratory study.

Reproductive Toxicity Studies

Study Type	Species	Route	Doses (mg/kg)	Findings
Segment I	Rat	Oral	6, 20, 60	At 60 mg/kg, decreased testes and epididymal weights, decrease in percent motile sperm, increased post-implantation loss. NOEL for male and female fertility and early embryonic development = 20 mg/kg.
Segment II range-finding	Rat	Oral	30, 100, 300	At 300 mg/kg death & total resorption. At 100 mg/kg increased post-implantation loss, decreased fetal weight & teratogenicity. No changes at 30 mg/kg.
Segment II	Rat	Oral	10, 30, 100	At 100 mg/kg, post-implantation loss and teratogenicity. At 30 mg/kg protruded tongue and shortened 13th rib. NOEL = 10 mg/kg.
Segment II range-finding	Rabbit	Oral	10, 30, 100	At 100 mg/kg, embryo-fetal toxicity; no reproductive changes at 10 or 30 mg/kg.
Segment II	Rabbit	Oral	6, 20, 60	At 60 mg/kg, slight delay in fetal development (ossification) and slight maternal toxicity. No teratogenicity.

Reproductive toxicity studies indicated that imatinib has a teratogenic potential in rats at doses ≥ 30 mg/kg. A dose of 10 mg/kg appeared to represent the no effect level (NOEL). In rats, doses ≥ 30 mg/kg induced embryo-fetal toxicity and/or teratogenicity (exencephaly, encephalocele, absent or reduced frontal, parietal and/or interparietal bones; dose-dependent protruded tongues) in surviving fetuses. In rabbits, there was no evidence of teratogenicity. Although testes and epididymal weights and percent motile sperm were decreased in male rats at 60 mg/kg, there were no effects on mating or on the number of pregnant females.

Three groups of time-pregnant female rats (n=24/group) were administered STI571 orally by gavage at dosages of 5, 15 and 45 mg/kg/day. The animals were treated from gestation day 6 through lactation day 20.

There was no maternal mortality. A red vaginal discharge was noted in the 45 mg/kg/day group on either day 14 or 15 of gestation. At this dose the number of stillborn pups was slightly increased while the number of viable pups and the number of pups dying between postpartum days 0 and 4 were decreased. In the F₁ offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. F₁ fertility was not affected while an increased number of resorptions and a decreased number of viable fetuses was noted at 45 mg/kg/day. The No Effect Level (NOEL) for both the maternal animals and the F₁ generation was 15 mg/kg/day (one-fourth the maximum human dose of 800 mg/day).

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 effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on GLEEVEC treatment should consult with their physician.

Juvenile Toxicology

In a juvenile development toxicology study in rats (day 10 to 70 post-partum) administered imatinib, a delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average pediatric exposure at the highest recommended dose of 340 mg/m². Transitory decreases in crown to rump length also were observed (between days 17 and 52 post-partum) in rats administered approximately 2X the highest recommended human pediatric dose of 340 mg/m². At this dose, shortened tibia and femur lengths were non-reversible in female rats while a trend towards reversibility was seen in male rats. Furthermore, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average pediatric exposure at the highest recommended dose of 340 mg/m². Another juvenile study demonstrated that rats administered imatinib resulted in premature growth plate closure.

Carcinogenesis and Mutagenesis

The genotoxic potential of imatinib was assessed in a battery of mutagenicity tests

Study Type	Findings
<i>In vitro</i> : Ames Salmonella and Escherichia/mammalian-microsome mutagenicity test 30.9 – 5000 µg/plate ± S9 (range)	Negative
<i>In vitro</i> : Gene mutation test with Chinese hamster cells V79 range: 7.41 - 200 µg/ml + S9 0.74 - 20 µg/ml – S9	Negative Negative
<i>In vitro</i> : Cytogenetic test on Chinese hamster cells CHO range: 31 - 125 µg/ml + S9 1.5 - 12.5 µg/ml – S9	Positive Negative
<i>In vitro</i> : Mouse lymphoma mutagenicity assay range: 0.98 - 62.5 µg/ml + S9 1.56 - 50 µg/ml – S9	Negative Negative
<i>In vivo</i> : Rat micronucleus Doses 25, 50 & 100 mg/kg	Negative

Imatinib was devoid of genotoxicity in bacterial and cellular assays for mutagenic effects. The rat micronucleus assay which detects clastogenic and aneugenic effects was also negative. Positive results were obtained in an *in vitro* assay for clastogenicity (chromosome aberration) in the presence of metabolic activation, but only at concentrations which resulted in significant cytotoxicity.

In a 2-year rat carcinogenicity study, imatinib was administered in feed at doses of 15, 30 and 60 mg/kg/day and resulted in a statistically significant reduction in the longevity of males rats at 60 mg/kg/day and females rats at ≥30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both rats sexes), chronic progressive nephropathy (females rats) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. The no observed effect levels (NOEL) for the various target organs with

neoplastic lesions were established as follows: 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 in rats, representing (approximately 0.5 to 4 times the human daily exposure at 400 mg/day (based on AUC), 0.3 to 2.4 times the human daily exposure at 800 mg/day (based on AUC), and 0.4 to 3.0 times the daily exposure in children at 340 mg/m² (based on AUC). The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, 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 only at 60 mg/kg/day.

Non-neoplastic histological lesions 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrGLEEVEC®

Imatinib mesylate tablets

Read this carefully before you start taking **GLEEVEC**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment. Ask if there is any new information about **GLEEVEC**.

What is GLEEVEC used for?

GLEEVEC is used to treat several **SOLID TUMOUR** or **BLOOD CANCER** indications. They are described in more detail below. Ask your doctor if you are not sure why GLEEVEC has been prescribed for you. GLEEVEC can be used in children for one indication.

BLOOD CANCERS

Adults and children two years old and older with a new diagnosis of:

Philadelphia chromosome-positive chronic myeloid leukemia (Ph-positive CML).

The cancer is in an early phase. It is called chronic phase.

- cancer of white blood cells
- certain abnormal cells (called myeloid cells) are growing out of control

BLOOD CANCERS

Adults

Philadelphia chromosome-positive chronic myeloid leukemia (Ph-positive CML)

- cancer of white blood cells
- certain abnormal cells (called myeloid cells) are growing out of control
- in chronic phase after failure of other treatment, it is called interferon.
- or in accelerated phase, or blast crisis. The blood cancer grows faster in these phases than in chronic phase.

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL)

- cancer of white blood cells
- certain abnormal cells (called lymphoblasts) are growing out of control
- first treatment in newly diagnosed Ph-positive ALL
- or when cancer has come back after treatment
- or when cancer was not successfully treated with other treatment.

Myelodysplastic/myeloproliferative diseases (MDS/MPD)

- a group of blood diseases

- too many abnormal blood cells are made
- GLEEVEC is used in a certain sub-type of these diseases.

Aggressive systemic mastocytosis (ASM), and systemic mastocytosis with an associated clonal haematological non-mast-cell disorder (SM-AHNMD)

- cancer of white blood cells
- certain abnormal cells (called mast cells) are growing out of control
- GLEEVEC is used in certain sub-types of these diseases.

Advanced hypereosinophilic syndrome (HES), and chronic eosinophilic leukemia (CEL)

- blood diseases
- certain abnormal blood cells (called eosinophils) are growing out of control
- GLEEVEC is used in a certain sub-type of these diseases.

SOLID TUMOURS

Adults

Dermatofibrosarcoma protuberans (DFSP)

- a cancer of the tissue beneath the skin
- some abnormal cells are growing out of control.

Gastrointestinal stromal tumours (GIST)

- a cancer of the stomach and bowels
- GLEEVEC is used:
 - in a sub-type of GIST
 - Where:
 - tumours cannot be removed with surgery
 - Where:
 - the cancer has spread to other parts of your body
 - Where:
 - tumours cannot be removed with surgery and the cancer has spread to other parts of your body.

Gastrointestinal stromal tumours (GIST):

- a cancer of the stomach and bowels
- GLEEVEC is used :
 - in a sub-type of GIST
- Where:
 - treatment after surgery is needed. This is called adjuvant treatment
- When:
 - the risk of tumours coming back is increased.

Serious Warnings and Precautions

Take GLEEVEC only under the care of a doctor who knows how to use anti-cancer drugs. They should be trained in how to treat solid tumours or blood cancers.

GLEEVEC can cause severe side effects,

- **Heart disease or problems** where your heart is unable to pump enough blood to meet the body's needs. These include:
 - **Left ventricular dysfunction**
 - **Congestive heart failure**
 - **Cardiogenic shock**
- **Water retention:** a build-up of water in your body
- **Side effects caused by water retention.** These include:
 - **Pleural effusion**
 - **Pulmonary edema**
 - **Pericardial effusion**
 - **Ascites**
- **Rhabdomyolysis:** a rapid breakdown of muscle. It may lead to sudden kidney failure.
- **Severe bleeding**
- **Liver disorder, jaundice, toxicity or failure.** In some patients, liver failure has led to death.
- **Gastrointestinal perforation:** a hole in the wall of your stomach, small or large bowel. In some patients, it has led to death.

The symptoms are listed in the “Serious side effects and what to do about them” box. It is found later in this leaflet.

How does GLEEVEC work?

GLEEVEC helps slow down or stop the growth of cancer cells in your body.

What are the ingredients in GLEEVEC?

Medicinal ingredients: imatinib mesylate

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, ferric oxide (red), ferric oxide (yellow), hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and talc.

GLEEVEC comes in the following dosage forms:

Tablet 100 mg, 400 mg

Do not use GLEEVEC if:

You are allergic to imatinib or any of the non-medicinal ingredients found in GLEEVEC.
You are breast-feeding. You must stop breast-feeding before taking GLEEVEC and 15 days after the last dose. It can get into breast milk and harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GLEEVEC. Talk about any health conditions or problems you may have,

or have ever had, including:

- heart, liver, kidney, stomach or bowel problems;
- bleeding problems;
- bleeding from your stomach, small bowel, or large bowel;
- had your thyroid removed and take a thyroid hormone such as levothyroxine;
- if you are pregnant or are planning to get pregnant. GLEEVEC can harm your unborn baby. Your healthcare professional might want you to take a pregnancy test before you take GLEEVEC. You should use highly effective birth control if you might get pregnant while taking GLEEVEC and for 15 days after ending treatment. If you become pregnant while taking GLEEVEC, or think you might be, tell your healthcare professional right away;
- **Tumour Lysis Syndrome (TLS)** is a serious side effect. It usually occurs after treatment of a large or fast-growing cancer. As tumour cells die certain chemicals are released into the blood. This may cause damage to organs. Before they start GLEEVEC, some people are at increased risk of Tumour Lysis Syndrome (TLS). If this is true for you, the doctor might give you treatments that may decrease the risk of TLS;
- if you are a man and are trying to have a child. Your healthcare professional may advise you not to start treatment with GLEEVEC while you are trying to have a child. Your healthcare professional may advise you to stop taking GLEEVEC before you try to have a child;
- if you have ever had or might now have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with GLEEVEC, hepatitis B may become active again, which can be fatal in some cases. Your doctor will check for signs of this infection before and during treatment with GLEEVEC.

Other warnings you should know about:

Driving and using machines: Before doing tasks which require special attention, wait until you are feeling well again. Blurred vision and being dizzy or drowsy can occur.

The following list contains some of the drugs that may interact with GLEEVEC. Tell your healthcare professional about ALL the medicines you take including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with GLEEVEC:

- some medicines used to treat fungal infections, like ketoconazole, itraconazole
- some medicines used to treat bacterial infections, like erythromycin, or clarithromycin
- some medicines used to treat epilepsy, like carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin, or primidone
- some medicines used to treat high cholesterol like simvastatin
- some medicines used to treat mental health disorders like pimozide
- some medicines used to treat high blood pressure or heart disorders. This includes metoprolol or a group of medicines called calcium channel blockers
- rifampicin a medicine used to treat tuberculosis (TB)

- St. John's Wort (*Hypericum perforatum*), a herbal product used to treat depression and other conditions
- dexamethasone, a medicine to treat inflammation
- cyclosporine, a medicine that keeps the immune system from rejecting a new organ after a transplant
- acetaminophen, a medicine used to reduce pain or fever — acetaminophen is also included in many cold and flu remedies, so check the label
- warfarin, a medicine used to treat or prevent blood clots
- levothyroxine, if you had your thyroid removed
- Do NOT drink grapefruit juice at any time while you are on GLEEVEC

If you are already taking GLEEVEC, tell your healthcare professional if you are prescribed a new medicine.

How to take GLEEVEC:

Take GLEEVEC only as prescribed for you by your doctor.

If your dose is 800 mg a day, **use only** the 400 mg tablets to make up your dose. This will reduce how much iron you get.

Take GLEEVEC by mouth, with food and a large glass of water.

You can take GLEEVEC in one of these two ways:

1. Swallow GLEEVEC:
 - a) Whole with a large glass of water.
 - b) If the 400 mg tablet is too large to swallow whole:
 - Break it in two pieces
 - Swallow each piece with water, one after the other
2. If you **cannot swallow** a 400 mg tablet broken in two or a 100 mg tablet:

Place the tablet in a glass with water or apple juice.

100 mg tablet: use 50 mL or one-quarter cup
 400 mg tablet: use 200 mL or a little less than 1 cup

 - Stir with a spoon to completely dissolve the tablet
 - Drink the whole drink right away
 - Rinse the glass with a little more water or juice and drink that too
 - No trace of the dissolved tablet should be left behind in the glass

Usual dose:

Your dose depends on if you are an adult or a child, and on your medical condition. Your healthcare professional will regularly monitor your condition. Your dose may change depending on how well GLEEVEC is working.

Age Group	Indication	Daily Dose	Instructions for Use
Adults	Philadelphia chromosome-positive chronic myeloid leukemia (Ph-positive CML)	<p>Usual dose: 400 mg or 600 mg</p> <p>Depending on how you respond to treatment you may get a higher or lower dose.</p> <p>If your dose is 800 mg per day</p>	<p>Take once a day</p> <p>Take twice a day. A 400 mg tablet in the morning and another 400 mg tablet in the evening.</p>
	<p>Gastrointestinal stromal tumours (GIST)</p> <p>Where:</p> <ul style="list-style-type: none"> tumours cannot be removed with surgery <p>Where:</p> <ul style="list-style-type: none"> the cancer has spread to other parts of your body <p>Where:</p> <ul style="list-style-type: none"> tumours cannot be removed with surgery, and the cancer has spread to other parts of your body 	<p>400 mg or 600 mg</p> <p>Depending on how you respond to treatment, you may get a higher or lower dose.</p> <p>If your dose is 800 mg per day</p>	<p>Take once a day</p> <p>Take twice a day. A 400 mg tablet in the morning and another 400 mg tablet in the evening</p>
	<p>Gastrointestinal stromal tumours (GIST), treatment after surgery when the risk of tumours coming back is high</p>	400 mg	Take once a day
	<p>Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)</p>	600 mg	Take once a day
	<p>Myelodysplastic/myeloproliferative diseases (MDS/MPD)</p>	400 mg	Take once a day
	<p>Aggressive systemic mastocytosis (ASM) and systemic mastocytosis with associated clonal hematological non-mast cell lineage disease (SM-AHNMD)</p> <ul style="list-style-type: none"> without a certain mutation (called D816V c-Kit). 	400 mg	Take once a day

	<ul style="list-style-type: none"> status of a certain mutation (called D816V c-Kit) is unknown. And, response to other therapies has not been good enough. associated with an abnormal increase in certain blood cells (called eosinophils). 	400 mg	
	Hypereosinophilic syndrome (HES) or chronic eosinophilic leukemia (CEL)	Starting dose: 100 mg. May be increased to 400 mg depending on how you respond to treatment.	Take once a day
	Dermatofibrosarcoma protuberans (DFSP)	800 mg	Take twice a day. A 400 mg tablet in the morning and another 400 mg tablet in the evening
Children: 2 years of age and older	Philadelphia chromosome-positive chronic myeloid leukemia (Ph-positive CML)	Depending on the child's weight and height, 100 mg to 600 mg	As prescribed by the doctor: Take once a day OR split into two doses, one in the morning and one in the evening

Overdose:

If you think you have taken too much GLEEVEC, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child:

- missed a dose OR threw up after taking the last dose. Do NOT take another dose or double dose. Instead, wait until it is time for your next dose.

What are possible side effects from using GLEEVEC?

These are not all the possible side effects you may feel when taking GLEEVEC. If you experience any side effects not listed here, contact your healthcare professional. Please also read the box called "Serious Warnings and Precautions".

Side effects may include:

- weight loss, no appetite, change in taste, dry mouth, sores in mouth
- heartburn, indigestion
- constipation, gas, feel bloated
- headache, dizziness
- difficulty sleeping, drowsiness
- weakness, feeling tired
- nosebleeds
- skin dry, itchy or less sensitive to touch
- skin more sensitive to sun
- night sweats, red in the face or other areas of the skin
- unusual hair loss or thinning
- muscle tension, cramps, pain
- bone pain
- joint pain and swelling
- tingling, pain, or numbness in hands, feet, legs
- cough

If any of these affects you severely, tell your healthcare professional.

GLEEVEC can cause abnormal blood test results. You may have blood thyroid hormone levels that are not normal. This occurs when your thyroid has been removed and you are on a drug such as levothyroxine.

Children who take GLEEVEC may have the following side effects more often than adults:

- Low blood levels of calcium, sugar, phosphates, albumin protein and sodium
- High blood levels of sugar

Your doctor will decide when to perform tests and will interpret the results.

While you are taking GLEEVEC, you will be weighed regularly.

Children and teenagers may grow more slowly when taking GLEEVEC. The healthcare professional will measure their growth at regular visits.

Your doctor may do blood and/or urine tests to check how well your kidneys are working. This will be done before you start taking GLEEVEC and during your treatment.

You have had hepatitis B (a viral infection of the liver) in the past.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	

VERY COMMON			
Water retention: rapid weight gain, swelling of your hands, ankles, feet, face, or eyelids, or your whole body.		√	
Decreased Platelets: bruising, bleeding, fatigue and weakness.		√	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms.		√	
Anemia (Decreased red blood cells): fatigue, loss of energy, weakness, shortness of breath.		√	
Musculoskeletal pain after discontinuing treatment with GLEEVEC: muscle pain, limb pain, joint pain and bone pain.		√	
COMMON			
Pleural effusion (fluid around the lungs): chest pain. Difficult or painful breathing, cough.			√
Pulmonary edema (fluid in the air spaces of the lungs): difficult breathing that is worse when you lie down. Cough up blood or blood-tinged froth.			√
Pericardial effusion (fluid around the heart): chest pain that feels better when you sit up rather than lie down. Feel light-headed or pass out. Irregular, fast, or forceful heartbeat. Difficult or painful breathing, cough.			√
Ascites (fluid in the abdomen): feeling of fullness, abdominal pain, shortness of breath.			√
Bleeding or swelling in the brain: severe headache.			

Weak or cannot move arms, legs or face. Difficulty talking, fainting or passing out. Dizziness, blurred vision, seizure (fit).			√
Pneumonia (infection in the lungs): shortness of breath. Difficult and painful breathing, cough, wheezing, or fever.			√
Shortness of Breath	√		
Chest Pain		√	
Inflammatory bowel disease: nausea, vomiting, diarrhea, abdominal pain, fever.		√	
Liver disorder, jaundice, toxicity, or failure: yellow skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.			√
Vomiting	√		
Diarrhea	√		
Nausea	√		
Pain in the abdomen	√		
Fever	√		
Less urine, urinate less often.		√	
Eye Infection (conjunctivitis): itchy, red eyes with discharge, and swelling.		√	
Increased tears in the eyes, dry eyes.	√		
Swelling around the eyes or in the eyelids.		√	
UNCOMMON			
Bleeding in the stomach or bowels: severe abdominal pain, vomit blood, black or bloody bowel movement, swelling of the abdomen. Feel dizzy or weak, loss of consciousness. Shortness of breath.			√

Gastrointestinal perforation (a hole in the wall of your stomach or bowels): severe abdominal pain, nausea, vomiting, chills or fever.			√
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath, tiredness, dry cough.			√
Acute respiratory failure: sudden worsening of shortness of breath, bluish color on skin, lips, and fingernails, irregular heartbeats, feel sleepy, loss of consciousness.			√
Low Blood Pressure: dizziness, fainting, light-headedness.		√	
Fainting or passing out		√	
Difficulty hearing		√	
Blood in urine		√	
Left ventricular dysfunction, Congestive heart failure (a weakness of the heart): tiredness, swollen ankles, shortness of breath especially when lying down.			√
Heart attack (blood flow stops to part of the heart): sudden chest pain or pressure or discomfort, feeling faint, shortness of breath, possibly irregular heartbeat.			√
Cardiogenic shock (heart is not able unable to pump enough blood to the organs of the body): breathe fast, fast heartbeat, loss of			√

consciousness, sweating, pale skin, cold hands or feet.			
Angina (not enough oxygen to the heart muscle): chest pain or pressure, usually coming during exercise or physical stress and relieved by rest.			√
Raynaud's syndrome: fingers and toes feel numb and cold in response to cold temperatures or stress.		√	
Cellulitis (infection under the skin): red, hot, painful and swollen area.		√	
Palmar-plantar erythrodysesthesia syndrome: red or swollen palms of the hands and soles of the feet. You might feel a tingling or burning pain as well.		√	
Tumour lysis syndrome nausea, shortness of breath, irregular heartbeat, cloudy urine, tiredness, or pain in joints.			√
RARE			
Eye Problems: blood in eye, trouble seeing, blurred vision.		√	
Pulmonary fibrosis (scarring of the lung tissues): shortness of breath, tiredness, dry cough.			√
Seizure		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center. Possibly swollen lips. Mild itching or burning.			√
Stevens Johnson syndrome,			

Toxic epidermal necrolysis (severe skin reaction): rash, red skin, red or purple skin patches possibly with blister or crust in the center, pus-filled rash, peeling skin, blisters on the lips, eyes, skin or in the mouth, itching, burning, flu-like feeling, fever.			√
Breakdown of red blood cells: pale skin, feeling tired or out of breath, dark urine.		√	
UNKNOWN FREQUENCY			
Allergic reactions: itch, rash, hives, swelling of the lips, tongue or throat, difficulty swallowing or breathing.			√
Drug reaction with eosinophilia and systemic symptoms (DRESS) (severe reaction to a medicine. Your skin and one or more of the organs in your body are involved. You may only have some of the side effects that are listed here): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinate less often, less urine.			√
Rhabdomyolysis (a rapid breakdown of muscle): unexplained muscle pain, tenderness or weakness. Dark brown urine.		√	
Blood clot in blood vessel: swelling, redness and pain in one part of the body.		√	
Gynecological disorder (problem in woman's reproductive system): pain in lower abdomen or		√	

unexpected blood from the vagina or both.			
Avascular necrosis / Hip osteonecrosis (break down and collapse of bone tissue.): pain and difficulty while walking.		√	
Chronic Kidney Impairment (reduced kidney function).		√	
Hepatitis B virus reactivation (an active viral infection of the liver): Fever, skin rash, joint pain and inflammation as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin or whites of eyes), pain in the upper right abdomen, pale stools and dark urine .		√	
Pseudoporphyria (painful blisters on sun-exposed skin; sunburn-type rash).		√	

These are not all the possible side effects you may feel when taking GLEEVEC. If you are bothered by a side effect not listed here, talk to your healthcare professional. If you have a symptom or side effect that begins to affect your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect \(http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php\)](http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of sight and reach of children.
- Keep tablets in their original package.
- Store the medication package at room temperature (15°C to 30°C).
- Protect the tablets from moist air. Make sure the tablets do not get wet.
- Use tablets before the expiry date on the box. Do NOT use tablets after that date.
- If a package is damaged or shows signs of tampering, do NOT use the tablets.

If you want more information about GLEEVEC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

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