PRODUCT MONOGRAPH

[Pr]GLEEVEC*

imatinib mesylate Tablets

imatinib 100 mg and 400 mg Tablets

Protein kinase inhibitor

GLEEVEC*, indicated for

- **the treatment of adult and pediatric patients with newly diagnosed, Philadelphia-chromosome-positive, chronic myeloid leukemia in chronic phase.**
- **the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).**

has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the conditional nature of the authorization.

GLEEVEC* has been issued non-conditional approval for the indications of:

- **Adult patients with Philadelphia chromosome-positive CML in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy).**
- **For use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL).**
- **Adult patients with relapsed or refractory Ph+ ALL as monotherapy.**
- **Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.**
- **Adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies.**
- **Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.**
- **Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).**

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Dorval, Quebec, H9S 1A9

Date of Revision:
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CONTROL No.: **105283**

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

Table of Contents

[Pr]GLEEVEC*

(imatinib mesylate)

PART I: HEALTH PROFESSIONAL INFORMATION

GLEEVEC*, indicated for

- the treatment of adult and pediatric patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase
- the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST)

has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

GLEEVEC* has been issued non-conditional approval for the indications of

- adult patients with Philadelphia chromosome-positive CML in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy).
- for use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)
- adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies.
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.
- adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

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). *For a complete listing see Dosage Forms, Composition section.*

INDICATIONS AND CLINICAL USE

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

Conditional approval in newly diagnosed CML, was based on hematologic and cytogenetic response rates (surrogate endpoints) that are reasonably likely to predict clinical benefit. There are no controlled trials that demonstrate clinical benefit in pediatric patients.

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

Non-conditional approval 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.

NOC • 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).

Non-conditional approval 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).

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

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

NOC • 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.

Non-conditional approval 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).

NOC • GLEEVEC* is also indicated for the treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactorily response to other therapies.

Non-conditional approval in adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation and in adult patients with ASM or SM-AHNMD[1] 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.

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

Non-conditional approval in adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement was based on hematologic and cytogenetic response rates (surrogate endpoints).

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

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

NOC/c • GLEEVEC* is also indicated for the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Conditional approval 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.

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).
- Severe hemorrhages may occur (See "Hemorrhage" section under WARNINGS and PRECAUTIONS).
- Fluid retention may occur (See 'Fluid Retention' 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 chronic myeloid leukemia or gastrointestinal stromal tumors.

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) 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*. 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 Table 1 and 2).** 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 and age >65 years. 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*.

All grade fluid retention/edema was reported in up to 61.7% for newly diagnosed CML patients and up to 76.2% for other CML patients across all clinical trials.

Gastrointestinal

Hemorrhage: In the newly diagnosed CML trial, 1.8% of patients had grade ¾ hemorrhage. In the GIST clinical trial 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. Caution should be exercised with the concomitant use of antiplatelet agents or warfarin.

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

Hematologic

Hematologic Toxicity: Treatment with GLEEVEC* is often associated with neutropenia or thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). 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, thrombocytopenia and anemia. These generally occur within the first several months of therapy (See DOSAGE AND ADMINISTRATION).

Hemorrhage

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

Hepatic/Biliary/Pancreatic

Liver failure: There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some cases the outcome was fatal.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with GLEEVEC*. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with GLEEVEC*. (See DOSAGE AND ADMINISTRATION). Patients with hepatic impairment should be closely

monitored. 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).

Toxicities From Long-Term Use: Because follow-up of most patients treated with imatinib is relatively short (<6 months), there are no long-term safety data on GLEEVEC* treatment. It is important to consider potential toxicities suggested by animal studies, specifically, *liver and kidney toxicity and immunosuppression.* 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.

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

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.

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: **Erythema multiforme** and **Stevens Johnson** syndrome have been reported in patients who have received GLEEVEC*.

Special Populations:

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. The potential risk for the fetus is unknown. Imatinib is teratogenic in animals, therefore, GLEEVEC* should not be administered to pregnant women unless clearly necessary. If used during pregnancy the patient should be apprised of the potential risk to the fetus. Women of childbearing potential must be advised to use effective birth control during treatment.

Nursing Women:

It is not known whether imatinib is excreted in human milk. In animals, imatinib and/or its metabolites were extensively excreted in milk, therefore, women who are taking GLEEVEC* should not breastfeed.

Pediatrics :
There is no experience with the use of GLEEVEC in pediatric patients with CML under 2 years of age. There is very limited experience with the use of GLEEVEC* in children under 3 years of age in other indications.

Geriatrics :

In the phase II studies, approximately 40% of patients were older than 60 years and 10% older than 70 years. There was a higher frequency of mild to moderate superficial edema in patients older than 65 years of age as compared to younger patients. No other age associated differences in safety profile were observed. The efficacy of GLEEVEC* was similar in all age groups studied.

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 WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS 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 WARNINGS AND PRECAUTIONS 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 WARNINGS AND PRECAUTIONS).

Thyroid-Stimulating Hormone (TSH) levels should be closely monitored in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC* (see WARNINGS AND PRECAUTIONS).

During treatment with GLEEVEC*, serum electrolytes should be regularly monitored for possible hypophosphatemia, hyperkalemia, hyponatremia in all CML patients; in addition in pediatric patients blood sugar, serum calcium and albumin should also be regularly monitored.

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.

Clinical Trial Adverse Drug Reactions

Chronic Myeloid Leukemia

Patients with advanced stages of chronic myeloid leukemia (CML) may have numerous confounding medical conditions that make causality of adverse events difficult to assess due to a variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medications.

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 ≥ 10% of patients in the clinical trials, regardless of relationship to therapy.

Table 1 Adverse experiences reported in newly diagnosed CML (≥10% of all patients)*

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**
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
Nausea	49.5	61.5	1.3	5.1
Muscle cramps	49.2	11.8	2.2	0.2
Musculoskeletal pain	47.0	44.8	5.4	8.6
Diarrhea	45.4	43.3	3.3	3.2
Rash and related terms	40.1	26.1	2.9	2.4
Fatigue	38.8	67.0	1.8	25.1
Headache	37.0	43.3	0.5	3.8
Joint pain	31.4	38.1	2.5	7.7
Abdominal pain	36.5	25.9	4.2	3.9
Nasopharyngitis	30.5	8.8	0	0.4
Hemorrhage	28.9	21.2	1.8	1.7
- GI hemorrhages	1.6	1.1	0.5	0.2
- CNS hemorrhages	0.2	0.4	0	0.4
Myalgia	24.1	38.8	1.5	8.3
Vomiting	22.5	27.8	2.0	3.4
Dyspepsia	18.9	8.3	0	0.8
Cough	20.0	23.1	0.2	0.6
Pharyngolaryngeal pain	18.1	11.4	0.2	0
Upper respiratory tract infection	21.2	8.4	0.2	0.4
Dizziness	19.4	24.4	0.9	3.8
Pyrexia	17.8	42.6	0.9	3.0
Weight increased	15.6	2.6	2.0	0.4
Insomnia	14.7	18.6	0	2.3
Depression	14.9	35.8	0.5	13.1
Influenza	13.8	6.2	0.2	0.2
Bone pain	11.3	15.6	1.6	3.4
Constipation	11.4	14.4	0.7	0.2
Sinusitis	11.4	6.0	0.2	0.2
Liver toxicity (including liver failure)	11.6	17.3	4.0	5.1
Rigors	9.3	34.0	0.2	0.8
Anxiety	9.6	11.8	0.5	2.6
Dyspnea	9.3	14.4	1.8	1.7
Pruritus	9.8	11.8	0.2	0.2
Influenza like illness	7.3	15.9	0	0.9
Night sweats	9.8	15.8	0.2	0.4
Anorexia	7.1	31.7	0	2.4
Sweating increased	5.8	14.8	0.2	0.4
Alopecia	4.9	22.3	0	0.6
Weight decreased	5.1	17.3	0.4	1.3
Asthenia	8.0	16.9	0.2	3.8
Dry mouth	2.9	10.9	0	0.2
Mucosal inflammation	1.1	10.3	0	3.2

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

Table 2 Adverse Experiences Reported in Other CML Clinical Trials (≥10% of allpatients in any trial)[1]

System Affected	Myeloid blast crisis N=260 (%)		Accelerated phase N=235 (%)		Chronic phase IFN failure N=532 (%)	
	All grades	CTC grade 3/4	All grades	CTC grade 3/4	All grades	CTC grade 3/4
Fluid retention*	71.5	11.2	76.2	6.4	68.6	3.6
- Superficial edemas*	66.2	5.8	73.6	3.4	67.5	2.1
- Other fluid retention events[2]*	22.3	6.2	14.9	3.8	7.1	1.7
Nausea	70.8	4.6	73.2	5.1	63.0	2.6
Muscle cramps*	28.5	1.2	46.8	0.4	61.7	1.7
Diarrhea	42.7	3.8	57.4	4.7	48.3	2.8
Vomiting	53.8	3.8	57.9	3.4	35.5	2.1
Rash and related terms*	35.8	4.6	47.2	5.1	47.4	3.2
Fatigue	29.6	4.2	45.5	3.8	47.9	1.1
Musculoskeletal pain*	41.9	8.8	49.4	8.5	38.3	2.4
Hemorrhages*	53.1	19.2	48.9	11.1	30.1	2.3
- GI hemorrhages*	8.5	3.8	6.0	4.7	2.1	0.4
- CNS hemorrhages*	8.8	6.9	3.4	2.6	1.7	1.3
Joint pain (Arthralgia)*	25.4	4.6	34.5	6.0	40.2	1.3
Headache	27.3	4.6	31.9	2.1	36.5	0.6
Abdominal pain*	29.6	6.2	33.2	3.8	31.8	1.1
Pyrexia	41.2	7.3	41.3	7.7	20.7	1.9
Dyspepsia	12.3		22.1		27.3	
Cough	14.2	0.8	27.2	0.9	19.9	
Myalgia			23.8	2.1	27.1	0.2
Asthenia	18.1	5.0	20.9	4.7	14.7	0.2
Dyspnea NOS	14.6	4.2	20.9	6.8	11.7	0.9
Dizziness	11.9	0.4	12.8		16.0	0.2
Night sweats	12.7	0.8	17.0	1.3	13.5	0.2
Pharyngitis			12.3		15.4	
Pruritis			13.6	0.9	13.9	0.8
Anorexia	14.2	1.5	17.4	1.7		
Constipation	15.8	1.5	15.7	0.9		
Insomnia	10.4		14.0		14.5	0.2
Chest pain					10.7	0.8
Pneumonia NOS	12.7	6.9	10.2	7.2		
Influenza					10.5	0.2
Rigors	10.4		12.3	0.4		
Hypokalemia	13.1	3.8				
Liver toxicity (including liver failure)			12.3	5.5		
Anxiety			11.9			
Nasopharyngitis			17.4		21.6	0.2
Sinusitis NOS			11.5	0.4		
Upper respiratory tract infection NOS			11.9	0.4	18.4	
Weight increase			17.4	5.1	32.3	6.8

Grouped events

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

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

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%), hypoglycaemia (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 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 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. 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 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)
Anaemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Gastrointestinal Stromal Tumors

GLEEVEC* was generally well tolerated in patients with 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 Reported in the GIST B2222 trial (≥10%) of all patients[1]

	All doses (n=147)	
	600 mg n=73	
	All Grades (%)	Grade ¾ (%)
Preferred Term		
Any Fluid retention	80.3	9.5
Superficial edema	78.9	5.4
Other fluid retention events [2]	13.6	5.4
Nausea	68.7	4.8
Diarrhea	64.6	4.8
Abdominal pain	57.1	8.8
Muscle cramps	52.4	0
Fatigue	50.3	1.4
Rash and related terms	45.6	3.4
Headache	36.1	0
Vomiting	36.7	4.1
Flatulence	32.0	0
Any Hemorrhage	29.9	8.2
Tumor Hemorrhage	2.7	2.7
Cerebral hemorrhage / subdural hematoma	0.7	0.7
Upper G-I tract bleeding/perforation	4.1	3.4
Other hemorrhage	24.5	2.7
Pyrexia	20.4	1.4
Musculoskeletal pain	33.3	3.4
Nasopharyngitis	23.8	0
Anemia	19.7	5.4
Insomnia	18.4	0.7
Lacrimation increased	17.0	0
Dyspepsia	15.0	0
Upper Respiratory Tract Infection	15.6	0
Liver Toxicity	12.2	6.8
Dizziness	11.6	0
Loose Stools	10.9	0
Operation	10.2	4.8
Pharyngolaryngeal Pain	9.5	0
Join Pain	12.9	0.7
Constipation	10.2	0.7
Anxiety	8.8	0
Back pain	24.5	0

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.
[2] Other fluid retention events included pleural effusion and ascites.

Second malignancies in GLEEVEC*- treated patients:

Table 6 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 **7** and **8**). 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 6) 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 was 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 them outcome was fatal (See DRUG INTERACTIONS).

Table 7 Newly occurring grade 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 8 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 ≥0.5 - 1.0 x 10^9/L), grade 4 <0.5 x 10^9/L), thrombocytopenia (grade 3 ≥10 - 50 x 10^9/L, grade 4 <10 x 10^9/L), anemia (hemoglobin ≥65 - 80 g/L, grade 4 <65 g/L), elevated creatinine (grade 3 >3-6 x upper limit normal range (ULN), grade 4 >6 x ULN), elevated bilirubin (grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase (grade 3 > 5-20 x ULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 3 >5-20 x ULN, grade 4 >20 x ULN).

Clinically relevant or severe abnormalities of the 12 patients treated with GLEEVEC* for DFSP in Trial B2225 are presented in Table 9.

Table 9 Laboratory Abnormalities Reported in DFSP Patients in Trial B2225

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

CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L), thrombocytopenia (Grade 3 ≥10 - 50 x 10^9/L, Grade 4 <10 x 10^9/L), anemia (Grade 3 ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 x upper limit normal range [ULN], Grade 4 >6 x ULN).

In 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 10).

Table 10 Laboratory Abnormalities in the GIST 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 Grade (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 10^9 /L, grade 2=1.0 - < 1.5 x 10^9 /L, grade 3 =0.5 -< 1.0 x 10^9/L, grade 4 <0.5 x 10^9/L), thrombocytopenia (grade 1 < LLN - 75.0 x 10^9/L, grade 2=50.0 - <75.0 x 10^9 /L, grade 3=10.0 - <50.0 x 10^9/L, grade 4 <10.0 x 10^9/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).

Post-Market Adverse Drug Reactions

The following less common (estimated 1%-10%), infrequent (estimated 0.1% - 1%), and rare (estimated less than 0.1%) adverse reactions have been reported in patients receiving GLEEVEC*.

Cardiovascular

Infrequent: cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness, thrombosis/embolism

Rare: pericarditis, pericardial effusion, cardiac tamponade, anaphylactic shock**.**

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Clinical laboratory tests

Infrequent: blood CPK increased, blood LDH increased

Dermatologic

Less common: dry skin, alopecia

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

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

Digestive

Less common: abdominal distention, gastroesophageal reflux, mouth ulceration

Infrequent: gastric ulcer, gastroenteritis, gastritis

Rare: colitis, diverticulitis, ileus/intestinal obstruction, pancreatitis, tumor hemorrage/tumor necrosis, gastrointestinal perforation (some fatal cases of gastrointestinal perforation have been reported).

General Disorders and Administration Site Conditions

Rare: tumor necrosis

Hematologic

Infrequent: pancytopenia

Rare: aplastic anemia

Hepatobiliary disorders

Infrequent: jaundice, hepatitis, hyperbilirubinaemia

Rare: hepatic failure, hepatic necrosis (some fatal cases of hepatic necrosis have been reported).

Hypersensitivity

Rare: angioedemia

Infections

Infrequent: sepsis, herpes simplex, herpes zoster

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

Musculoskeletal
Less common: joint swelling
Infrequent: sciatica, joint and muscle stiffness
Rare: Avascular necrosis/hip osteonecrosis

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

Renal
Infrequent: renal failure, urinary frequency, hematuria

Reproductive
Infrequent: breast enlargement, menorrhagia, sexual dysfunction

Respiratory
Rare: interstitial pneumonitis, pulmonary fibrosis
Infrequent: acute respiratory failure (fatal cases have been reported in patients with advanced respiratory disease, severe infections, severe neutropenia and other serious concomitant clinical conditions).

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

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, oxcarbamazepine, 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 imatinib and a product containing St. John's wort led to a 30-32% 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 11 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

Imatinib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5- fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering GLEEVEC* with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide), (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 Cmax 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 imatinib and metoprolol clinical monitoring should be considered.

In vitro data suggest that imatinib 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 (Ki value of 58.5 µmol/L) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when co administered with GLEEVEC*. No specific studies in humans have been performed and caution is recommended.

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.

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. 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. The dose recommendation is currently based on a small number of pediatric patients. (See CLINICAL TRIALS SECTION AND ACTION AND CLINICAL PHARMACOLOGY SECTION). There is no experience with the use of GLEEVEC* in pediatric patients under 2 years of age.

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

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/m^2/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.

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. If c-Kit mutational status is not known or unavailable, treatment with GLEEVEC* 400 mg/day may be considered for patients with ASM or SM-AHNMD 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-PDGFRα, 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

Dermatofibrosarcoma Protuberans (DFSP)

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

Gastrointestinal stromal tumors (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.

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

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 Hepatotoxicity and Other Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicty 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 children, daily doses can be reduced under the same circumstances from 340 mg/m^2/day to 260 mg/m^2/day.

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. The dose should be reduced if not tolerable, or 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 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-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1.0 $x10^9$/L and/or platelets < 50 $x10^9$/L	1. Stop GLEEVEC* until ANC ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L. 2. Resume treatment with GLEEVEC* at previous dose (i.e. before severe adverse reaction).
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	1. Stop GLEEVEC* until ANC. 1.5 $x10^9$/L and platelets. 75 $x10^9$/L. 2. Resume treatment with GLEEVEC* at the original dose of 400 mg or 600 mg (i.e. before severe adverse reaction). 3. If recurrence of ANC < 1.0 $x10^9$/L and/or Platelets < 50 $x10^9$/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	1. Stop GLEEVEC* until ANC ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L. 2. Resume treatment with GLEEVEC* at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 $x10^9$/L and/or platelets < 50 $x10^9$/L, repeat step 1 and resume GLEEVEC* at reduced dose of 260 mg/m^2/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	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 ≥ 1 $x10^9$/L and platelets ≥ 20 $x10^9$/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	1. Stop GLEEVEC* until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with GLEEVEC* at 600 mg. 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume GLEEVEC* at reduced dose of 400 mg.

ANC: absolute neutrophil count
[1]occurring after at least 1 month of treatment

OVERDOSAGE

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

A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1200 mg of GLEEVEC* daily for 6 days. Treatment was temporarily interrupted and complete reversal of all abnormalities occurred within one week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse events. Another patient developed severe muscle cramps after taking 1,600 mg of GLEEVEC* daily for 6 days. Complete resolution of muscle cramps occurred following interruption of treatment and treatment was subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of GLEEVEC*on day 1 and 1,200 mg on day 2. Treatment was interrupted, no adverse events occurred and the patient resumed treatment.

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 the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating *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 IC_{50} of the mutation, and others requiring alternative treatment strategies.

Recent i*n-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 PgP 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 ∞_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 ^{14}C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Plasma pharmacokinetics: Following oral administration in healthy volunteers, the $t_{½}$ 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/m^2/day (n=6), 340 mg/m^2/day (n=11), 440 mg/m^2/day (n= 8) and 570 mg/m^2/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 AUC_{0-24} on Day 8 versus Day 1 at the 340 mg/m^2/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 AUC_{0-24} ranged from 21% (260 mg/m^2/day) to 68% (570 mg/m^2/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 12), 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 PRECAUTIONS & DOSAGE AND ADMINISTRATION).

Table 12: 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 13 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, or 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 DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Table 13 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 μM, 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^{o}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) 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) 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

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

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

^{Pr}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

GLEEVEC*, indicated for

- the treatment of adult and pediatric patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase
- the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST)

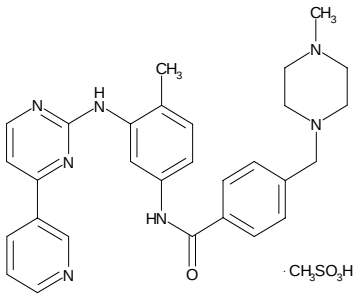
has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

GLEEVEC* has been issued non-conditional approval for the indications of

- adult patients with Philadelphia chromosome-positive CML in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy)
- for use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)
- adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies.
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.
- adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

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	$C_{29}H_{31}N_7O$. 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
pKa:	7.8, 3.8, and 3.3
Distribution coefficient:	> 100 (n-octanol/phosphaste buffer pH 6.8 medium at 37±1°C). Log D = 3.5

CLINICAL TRIALS

Chronic Myeloid Leukemia

NOC/c *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/m^2/day subcutaneously. In addition, subcutaneous Ara-C, (20 mg/m^2/day), was administered for ten days every month until a complete cytogenetic response 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 10^9/L at diagnosis to 19x10^9/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 20x10^9/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 5 years after the last patient had been recruited, the median duration of first-line treatment was 60 months and 8 months in the GLEEVEC* and IFN + Ara-C arms, respectively, with 69% of patients randomized to GLEEVEC* still receiving first-line treatment. Due to discontinuations and crossover, only 3% 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 (359/553), the reasons for crossover to the GLEEVEC* arm were intolerance to treatment (N=144, 40.1%), 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 14.

Table 14 Response in newly diagnosed CML study (First Line) (60-month data)

Best response rates	GLEEVEC* n=553	IFN + Ara-C n=553
Hematological response[1]		
CHR rate n (%)	534 (96.6)*	313 (56.6)*
[95% CI]	[94.7,97.9]	[52.4, 60.8]
Cytogenetic response[2]		
Major Cytogenetic response n (%)	471 (85.2)*	93 (16.8)*
[95% CI]	[81.9, 88.0]	[13.8, 20.2]
Unconfirmed[3]	490 (88.6)*	129 (23.3)*
Complete Cytogenetic Response n (%)	404 (73.1)*	35 (6.3)
Unconfirmed[3]	454 (82.1)	64 (11.6)
Molecular response[4]		
Major response at 12 months (%)	40	2*
Major response at 24 months (%)	54*	NA[5]

*p<0.001, Fischer's exact test

1 **Hematological response criteria** (all responses to be confirmed after ≥4 weeks): WBC<10x10^9/L; platelet <450x10^9/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 5 years of follow-up, there were 86 (15.6%) progression events in the GLEEVEC* arm: 35 (6.3%) involving progression to AP/BC, 28 (5.1%) loss of MCyR, 14 (2.5%) loss of CHR or increase in WBC and 9 (1.6%) CML unrelated deaths. In contrast, there were 155 (28.0%) events in the IFN+Ara-C arm of which 128 occurred during first-line treatment with IFN+Ara-C. These progression events in the IFN + Ara-C arm included 58 (10.5%) involving progression to AP/BC, 29 (5.2%) loss of MCyR, 47 (8.5%) loss of CHR, 17 (3.1%) increase in WBC, and 4 (0.7%) CML-unrelated deaths.

The estimated rate of progression-free survival at 60 months was 83.2% with [95% CI: 79%, 87%] in the GLEEVEC* arm and 64.1% with [95% CI: 59%, 69%] in the IFN+Ara-C arm (p<0.001) (Figure 1).

The estimated rate of patients free of progression to AP or BC at 60 months was significantly higher in the GLEEVEC* arm compared to the IFN+Ara-C arm (92.9% with [95% CI: 90, 96] versus 86.2% with [95% CI: 82, 90], (p<0.001 respectively)) (Figure 2).

Figure 1 Time to progression (ITT principle)

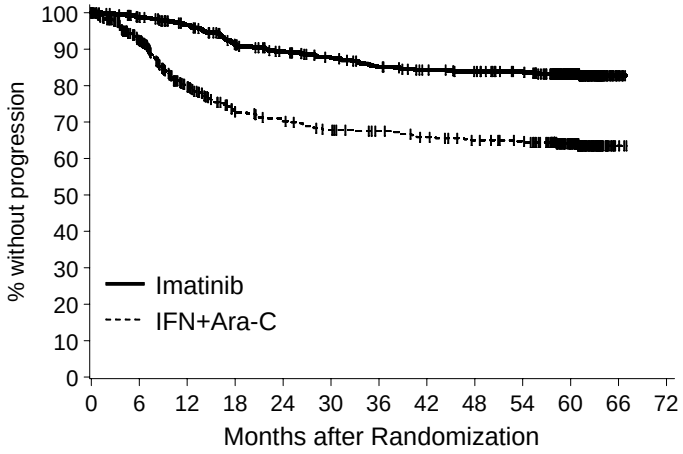
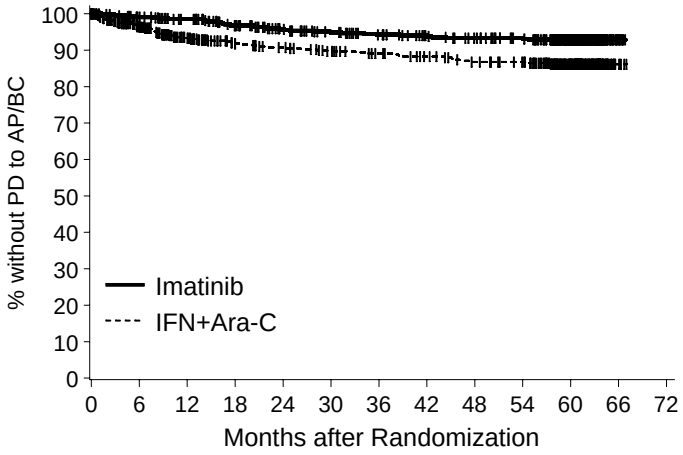


Figure 2 Time to progression to AP or BC (ITT principle)



A total of 57 (10.3%) and 73 (13.2%) patients died in the GLEEVEC* and IFN+Ara-C groups, respectively. At 60 months the estimated overall survival is 89.4% [95% CI: 86, 92] vs. 85.6% [95% CI: 82, 89] in the randomized GLEEVEC* and IFN+Ara-C groups, respectively (p=0.049, 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 CML:

A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase have been enrolled in an open-label, multicenter, single arm phase II trial. Patients were treated with GLEEVEC 340 mg/m^2/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 78% after 8 weeks of therapy. Those patients for whom cytogenetics was evaluable (33/51) developed a complete cytogenetic response (CCyR) of 65% which is comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16% adding up to a Major Cytogenetic response (MCyR) rate of 81%. 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.

NOC *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 ≥ 25 x10^6 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 15. 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 15). 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 ≥ 100 x 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 15 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 response[1]	**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 response[2]			
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 response[3]			
Unconfirmed	48%	20%	7%
Confirmed	38%	16%	2%

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

CHR: Chronic phase study [WBC <10 x10^9/L, platelet <450 x10^9/L, myelocytes+metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC≥1.5 x10^9/L, platelets ≥100 x10^9/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: same criteria as for CHR but ANC ≥1 x10^9/L and platelets ≥20 x10^9/L (accelerated and blast crisis studies)

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

BM=bone marrow, PB=peripheral blood

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

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

The median time to hematologic response was 1 month.

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

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

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

NOC 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 16 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 17 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)

[1]43/46 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

NOC 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 an 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 (0.8-26.7) 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 18.

Table 18 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

NOC 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-PDGFRα 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 19.

Table 19 Response in ASM

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFRα 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

NOC 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 20.

Table 20 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
Positive FIP1L1-PDGFRα fusion kinase	69	69 (100%)	0 (0%)
Negative FIP1L1-PDGFRα fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Overall totals	176	107 (61%)	16 (9%)

NOC 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 21.

Table 21 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/m^2/daily, subsequently increased to 520 mg/m^2/daily. The approved pediatric dose in CML is 340 mg/m^2/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.

NOC/c ***Gastrointestinal Stromal Tumors***

One phase 2, open-label, randomized multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. 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 22.

Table 22 Best Tumor Response in Trial STIB2222 (GIST)

Best response	All doses (n=147) 400 mg n= 73 600 mg n=74 n (%)
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 12-23). Median time to treatment failure in responders is 122 weeks (95% CI 106 - 147), while in the overall population is 84 weeks (95% CI 71 - 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

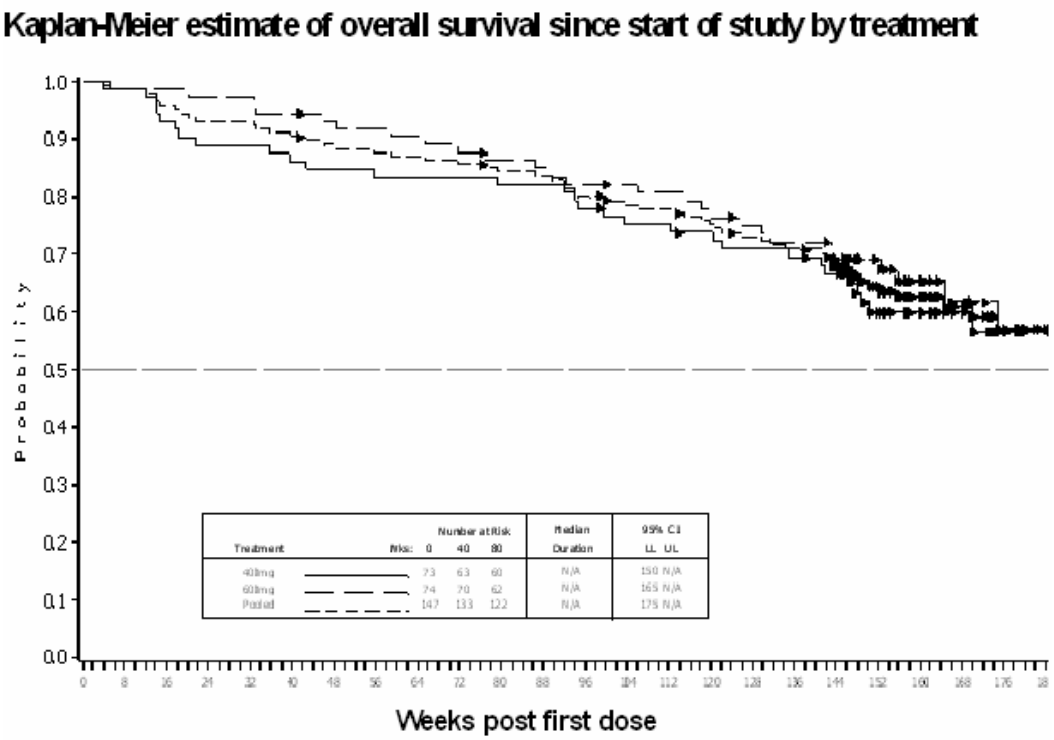
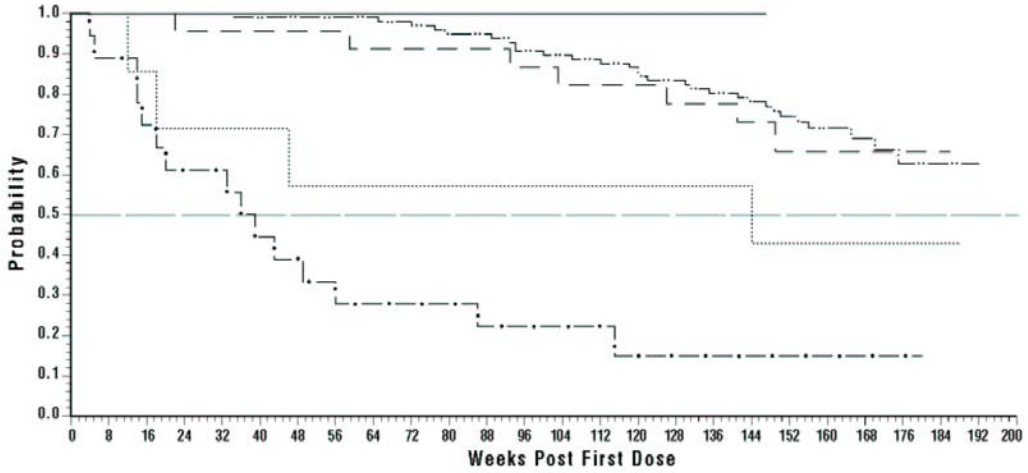


Figure 4: Kaplan-Meier estimate of overall survival since start of study by best response.



Best Response	Wks:	Number at Risk 0	40	80	Median Duration	95% CI LL	UL
CR		1	1	1	N/A	N/A	N/A
PR		98	97	92	N/A	N/A	N/A
SD		23	22	20	N/A	149	N/A
PD		18	8	5	38 Wks	18	56
UNK		7	5	4	144 Wks	18	N/A

In two randomized clinical studies (Study B2222 and an intergroup Study S0033) the daily dose of GLEEVEC* was escalated to 800 mg in patients progressing at the lower daily doses of 400 mg. A total of 103 patients escalated their dose to 800 mg daily; 6 patients achieved a partial response and 21 patients a stabilization of their disease after dose escalation.

Study S0033 showed no significant differences in efficacy between a starting dose of 400 mg and a starting dose of 800 mg daily. The clinical benefit of dose escalation to 800 mg after progression remains uncertain. The European-Australian phase III randomized trials, also comparing imatinib 400 mg versus 800 mg/day as starting dose, did not show significant differences in terms of response or overall survival. However, the trial reported a statistically significant advantage in progression-free survival with the higher dose of GLEEVEC*. A total of 133 patients were dose escalated to 800 mg following disease progression at the 400 mg starting dose. Of these patients, 3 patients achieved a partial response and 36 patients a stabilization of their disease. The dose escalation in this study led to a significant increase in anemia and fatigue, although less cases of neutropenia were reported after the dose escalation to 800 mg.

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	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. ≥ 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. ≥ 5 mg/kg: Salivation, presence of oral red substance, chromodacryorrhea, increased incidence/frequency of chromorhinorrhea. Most changes were reversible or partially reversible by the end of the recovery period. NTEL = 5 mg/kg.
2-week	Dog	p.o.	10, 30 & 100	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.
13 weeks	Dog	p.o.	3, 10, 30 & 100 reduced to 50	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.
4 weeks (exploratory)	Dog	p.o.	100	Moribundity (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.
2 weeks	Monkey	p.o.	10, 30,100 & 300 reduced to 200	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

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. $AUC_{(0\text{-}18)}$: 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 $\geq$ 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 $\geq$ 200 mg/kg in the rat and $\geq$ 30 mg/kg in the dog. A slight to moderate reduction in spermatogenesis was observed in the dog $\geq$ 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 $\geq$ 60 mg/kg and in dogs at 100$\rightarrow$50 mg/kg/day. Diarrhea was observed in the dog at oral doses $\geq$ 3mg/kg/day. Emesis was observed at oral doses of $\geq$ 30 mg/kg in the dog and $\geq$ 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 $\geq$ 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 $\geq$ 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$\rightarrow$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 $\geq$ 10 mg/kg, most pronounced at the100/50 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 F_1 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. F_1 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 F_1 generation was 15 mg/kg/day (one-fourth the maximum human dose of 800 mg/day).

Carcinogenesis and Mutagenesis

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

Study Type		Findings
In vitro: Ames Salmonella and Escherichia/mammalian-microsome mutagenicity test 30.9 – 5000 µg/plate ± S9 (range)		Negative
In vitro : Gene mutation test with Chinese hamster cells V79		
range:	7.41 - 200 µg/ml + S9	Negative
	0.74 - 20 µg/ml – S9	Negative
In vitro: Cytogenetic test on Chinese hamster cells CHO		
range:	31 - 125 µg/ml + S9	Positive
	1.5 - 12.5 µg/ml – S9	Negative
In vitro: Mouse lymphoma mutagenicity assay		
range:	0.98 - 62.5 µg/ml + S9	Negative
	1.56 - 50 µg/ml – S9	Negative
In vivo: 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/m^2 (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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PART III:
CONSUMER INFORMATION

[Pr]GLEEVEC*

imatinib mesylate Tablets

imatinib 100 mg and 400 mg Tablets

GLEEVEC*, for use in the treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+CML) in chronic phase, also for use in the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST), has been approved with conditions, pending the results of studies to verify its clinical benefit.

For more information, patients are advised to contact their health care provider.

GLEEVEC* has received an approval for use in the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy); for use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL); in adult patients with relapsed or refractory Ph+ ALL as single agent; in adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; in adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies; adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement; and in adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

[Pr]GLEEVEC*
(imatinib mesylate)

This leaflet is part III of a three-part "Product Monograph" published when GLEEVEC* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GLEEVEC*. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using GLEEVEC*

Keep this leaflet. You may need to read it again.

This medicine has been prescribed only for you. Do not give it to anybody else or use it for any other illnesses.

ABOUT THIS MEDICATION

What the medication is used for:

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

Leukemia is a cancer of white blood cells. (normal white cells usually help the body to fight infection). Chronic myeloid leukemia is a form of leukemia in which certain abnormal white cells, named myeloid cells, start growing out of control.

- 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).

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

Acute lymphoblastic leukemia is a form of leukemia in which certain abnormal white cells named lymphoblasts start growing out of control.

- 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.

MDS/MPD diseases are a group of blood diseases in which some blood cells start growing out of control.

- GLEEVEC* is also indicated for the treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies.

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

ASM is a cancer in which certain blood cells (named "mast" cells) start growing out of control.

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

HES and/or CEL are blood diseases in which some blood cells (named "eosinophils") start growing out of control.

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

DFSP is a cancer of the tissue beneath the skin in which some cells start growing out of control.

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

GIST is a cancer of the gastrointestinal system (stomach and the bowels). It arises from uncontrolled cell growth of the supporting tissue of this system.

What it does:

GLEEVEC* specifically targets the activity of certain enzymes called tyrosine kinases that play an important role within certain cancer cells.

GLEEVEC* inhibits the growth of abnormal white blood cells by blocking an enzyme involved in the development of certain cancers such as Ph+CML and Ph+ALL.

GLEEVEC* inhibits the uncontrolled growth cells of the supportive tissues involved in the development of cancers of the gastrointestinal system (stomach and the bowels).

When it should not be used:

If you are allergic (hypersensitive) to imatinib mesylate or any of the other ingredients of GLEEVEC* listed under section *What the important nonmedicinal ingredients are.*

What the medicinal ingredient is:

GLEEVEC* contains an active ingredient called imatinib mesylate.

What the important nonmedicinal ingredients are:

GLEEVEC (imatinib mesylate) 100 mg tablets :*
Each tablet contains 100 mg of imatinib (as mesylate) 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) 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.

What dosage forms it comes in:
GLEEVEC* is supplied as a tablet.

GLEEVEC (imatinib mesylate) 100 mg tablets*
GLEEVEC (imatinib mesylate) 400 mg tablets*

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

GLEEVEC* should only be prescribed to you (or your child) by a doctor who is experienced in the use of anti-cancer drugs. Serious and/or common side effects that may occur with GLEEVEC* include:

- Severe heart failure and decrease in the amount of blood pumped by the heart,
- Serious bleeding,
- Fluid retention.

Before you (or your child) take GLEEVEC* talk to your doctor or pharmacist:

- if you have or ever have had a liver, kidney or heart problem,
- if you are or plan to get pregnant. Women who might get pregnant are advised to use an effective method of birth control while taking GLEEVEC*,
- if you are breast-feeding,
- if you had your thyroid removed and are receiving treatment with a thyroid hormone such as levothyroxine.

While taking GLEEVEC*, if you feel dizzy or if you have blurred vision, do not drive a vehicle or operate any tools or machinery.

Use in children

There is no experience with the use of GLEEVEC* in children under 2 years of age.

INTERACTIONS WITH THIS MEDICATION

Inform your doctor or pharmacist before or while taking GLEEVEC* if you are taking or have recently taken any other medicines, even those not prescribed by a doctor or natural health products, including nonprescription drugs.

Drugs that interact with GLEEVEC* include:

- some medicines used to treat infections such as ketoconazole, itraconazole, erythromycine, or clarithromycin,
- some medicines used to treat epilepsy such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin, or primidone,
- some medicines used to treat high cholesterol such as simvastatin,
- some medicines used to treat mental disorders such as pimozide,
- some medicines used to treat high bood pressure or heart disorders such as calcium channel blockers or metoprolol,
- rifampicin, a medicine used to treat tuberculosis
- St. John's Wort - a herbal product used to treat depression and other conditions (also known as *Hypericum Perforatum),*
- dexamethasone, an anti-inflammatory medicine,
- cyclosporine, an immunosuppressant medicine,
- acetaminophen, a medicine used to relieve the pain or to reduce fever,
- warfarin, a medicine used to treat blood coagulation disorders (such as blood clots or thromboses).

You should also tell your doctor **if you are already taking GLEEVEC*** and you are prescribed a new medicine you have not previously taken during GLEEVEC* treatment.

In addition, do not drink grapefruit juice while you are being treated with GLEEVEC*.

PROPER USE OF THIS MEDICATION

How to take GLEEVEC*

Adults

Usual adult dose:

- 400 mg/day in newly diagnosed CML or Chronic phase CML.
- 600 mg/day in accelerated phase and blast crisis CML.
- 400 mg/day or 600 mg/day for GIST.
- 600 mg/day for Ph+ALL.

For CML and GIST, your doctor may prescribe a higher or lower dose depending on how you respond to treatment. If a dose of 800 mg is administered, it should be taken as 400 mg twice a day, in the morning and in the evening.

- **If you are being treated for MDS/MPD**: the starting dose in adult patients with myelodysplastic/myeloproliferative diseases is 400 mg/day.

- **If you are being treated for ASM**: the starting dose in adult patients with aggressive sub-types systemic mastocytosis (ASM and SM-AHNMD) without the D816V c-Kit mutation or with c-Kit mutational status unknown is 400 mg, to be taken once a day. For patients with ASM or SM-AHNMD associated with eosinophilia, the starting dose is 100 mg once a day.

- **If you are being treated for HES/CEL:** the usual starting dose in adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) is 100 mg to be taken once a day.

  For ASM/SM-AHNMD and HES/CEL patients receiving 100 mg/day, your doctor may decide to increase the dose to 400 mg once a day depending on how you respond to treatment.

- **If you are being treated for DFSP**: the starting dose is 800 mg/day, to be taken as 400 mg twice a day, in the morning and in the evening.

Children

The doctor will tell you how many tablets of GLEEVEC* to give your child. The amount of GLEEVEC* given, will depend on your child's condition, and also his or her body weight and height.

Usual dose for children (2 years of age and older): 340 mg/m^2 body surface area/day, rounded up to the nearest 100 mg and not to exceed 600 mg/day.

The treatment can either be given to your child as a once-daily dose or alternatively the daily dose can be split into two administrations (one in the morning and one in the evening).

GLEEVEC* should be taken during a meal and with a large glass of water. Avoid drinking grapefruit juice while being treated with GLEEVEC*. Swallow the tablet whole. The 400 mg tablet can be broken in half.

If you (or your child) cannot swallow the tablet(s), you can place them in water or apple juice, use 200 mL for 400 mg tablet or 50 mL for 100 mg tablet. Stir with a spoon to completely disintegrate the tablet(s), then drink the whole content immediately. Rinse the container with water or apple juice and drink it to make sure no trace of disintegrated tablet(s) is left.

When and how long to take GLEEVEC*

Your doctor will determine when you will be given GLEEVEC* and for how long you should receive it. Do not exceed the recommended dosage and make sure you take GLEEVEC* for as long as prescribed.

What if you miss a dose

If you forget to take a dose of GLEEVEC*, take the missed dose as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosage schedule. Do not double doses.

Overdose

If you think you may have taken more GLEEVEC* than you should (overdosage is known or suspected), contact your doctor or the nearest poison control center immediately. You may require medical attention.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects

Very common side effects that can occur during treatment with GLEEVEC* are weight gain, headache, nausea, vomiting, diarrhea, indigestion, rash, muscle spasms and cramps, pain in the muscles and bones, joint swelling and joint pain.

Other possible side effects of GLEEVEC* are anorexia, depression, dizziness, taste disturbance, numbness of the hands or feet, difficulty sleeping, red eye (conjunctivitis), blurred vision, increased tear production, chest pain on deep breathing (pleurisy), nose bleeds, abdominal pain or distension, gas (flatulence), constipation, dry mouth, itching, dry skin, unusual hair loss or thinning, night sweats, fatigue, weakness, and increased muscle tension, hypersensitivity (allergies).

In pediatric patients, higher frequencies of the following blood levels were observed compared to adult patients:

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

-high blood levels of sugar.

Your doctor will tell if your blood tests results changed abnormally.

Abnormal thyroid hormone levels (hypothyroidism) were observed in patients whose thyroid has been removed and who are receiving treatment with a thyroid hormone such as levothyroxine.

Your doctor will tell you if your thyroid hormone levels changed abnormally.

Tell your doctor if you experience any of the events listed above.

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	rapid weight gain, swelling, of extremities (calves, ankles), generalised swelling such as swelling of the face (signs of water retention).		√
	weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, severe chills, sore throat, mouth ulcers. Treatment with GLEEVEC* may reduce the number of white cells in your blood, which may lead to infection (signs of thrombocytopenia, neutropenia, pancitopenia[1]).		√
Uncommon	crushing, chest pain, irregular heart rhythm (sign of heart disorders such as heart failure, cardiac tamponade[2], pericarditis[2])		√
	Nausea, loss of appetite, light-coloured urine or yellowing of your skin or eyes go yellow (sign of liver disorders such as hepatic necrosis[3]).		√
	skin shows unusual peeling		√
	severe painful swelling of an extremity.		√
	vomit blood, find blood in your stools or urine, have black stools or have severe abdominal pain (signs of gastrointestinal hemorrhage).		√
Rare	severe abdominal pain (a sign of intestinal obstruction).		√
	cough, or difficulty breathing (such as acute respiratory failure[4]), painful breathing.		√
	skin shows blistering.		√
	pain in your hips or have difficulty walking (such as avascular necrosis/hip osteonecrosis).		√
	Light-headedness, dizziness or fainting (signs of anaphylactic shock)		√
	Severe headache (signs of nervous system disorders)		√
	Sudden vision impairment (sudden change in your eyesight)		√

[1] Pancytopenia was uncommonly observed.
[2] Cardiac tamponade and pericarditis were rarely observed.
[3] hepatic necrosis was rarely observed.
[4] acute respiratory failure was uncommonly observed.

This is not a complete list of side effects. If you have any unexpected effects after receiving GLEEVEC, contact your doctor or pharmacist*

HOW TO STORE GLEEVEC*

Keep GLEEVEC* out of the reach and sight of children.

- Store GLEEVEC* at room temperature (15- 30°C). Protect tablets from moisture.
- Store GLEEVEC* in the original package.
- Do not use GLEEVEC* after the expiry date shown on the box.
- Do not use any GLEEVEC* pack that is damaged or shows signs of tampering.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883

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