NOVARTIS

Regulatory Affairs

GLIVEC®

(imatinib mesilate)

100 mg and 400 mg Film-coated Tablets
100 mg Hard Capsules

International Package Leaflet

IPL Author:	Sree Lalitha Narayana
CDS Author(s):	Amrish Huddar
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Glivec®

BCR-ABL tyrosine kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Film-coated tablets

GLIVEC® 100 and 400 mg film-coated tablets

Note: Glivec® is known as Gleevec® (imatinib mesilate) tablets in the US, Canada and Israel.

100 mg tablets, divisible

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

400 mg tablets, not divisible

Very dark yellow to brownish orange, ovaloid, biconvex with beveled edges. De-bossed with “NVR” on one side and “SL” on the other side.

Very dark yellow to brownish orange, ovaloid, biconvex with beveled edges. De-bossed with “glivec” on one side.

400 mg tablets, divisible

Very dark yellow to brownish orange, ovaloid, biconvex with beveled edges. De-bossed with “400” on one side and score on the other side and “SL” on each side of the score.

Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with beveled edges, de-bossed with “gleevec” on one side and score on the other side.

Hard capsules

100 mg capsules

White to yellow powder in an orange to greyish-orange opaque capsule, marked “NVR SI”.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance

Film-coated tablets

Each film-coated tablet contains 100 or 400 mg imatinib (as mesilate beta crystals).

Hard capsules

Each capsule contains 100 mg imatinib (as mesilate beta crystals).

Excipients

100 and 400 mg (divisible or non-divisible) film-coated tablets

Tablet content: Cellulose microcrystalline, Crospovidone, Hypromellose, Magnesium stearate, Silica colloidal anhydrous.

Coating content: Hypromellose, Macrogol, Talc, Iron oxide, red (E 172), Iron oxide, yellow (E 172).

100 mg capsules

Capsule content: Cellulose microcrystalline; Crospovidone; Magnesium stearate; Silica colloidal, anhydrous.

Capsule shell: Gelatin; Iron oxide, red (E 172); Iron oxide, yellow (E 172); Titanium dioxide (E 171).

Printing ink: Iron oxide, red (E 172).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Glivec is indicated for the

- treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) (for pediatric use see section DOSAGE REGIMEN AND ADMINISTRATION).
- treatment of adult and pediatric patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy (for pediatric use see section DOSAGE REGIMEN AND ADMINISTRATION).
- treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
- treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- treatment of adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL).
- treatment of adult patients with Kit+ (CD117) unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- adjuvant treatment of adult patients following resection of Kit+ GIST.
- treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

DOSAGE REGIMEN AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies and malignant sarcomas, as appropriate.

The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.

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

For patients (e.g.pediatric patients) unable to swallow the capsules, their content may be diluted in a glass of still water or apple juice. Since studies in animals have shown reproductive toxicity, and the potential risk for the human fetus is unknown, women of child-bearing potential, who open capsules should be advised to handle contents with caution and avoid skin-eye contact or inhalation (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL). Hands should be washed immediately after handling open capsules.

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

Monitoring of response to Glivec therapy in Ph+ CML patients should be performed routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

General target population:

Dosage in CML

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

Dose increase from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological 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 hematological and/or cytogenetic response.

See section on special populations for pediatric patients.

Dosage in Ph+ ALL

The recommended dose of Glivec is 600 mg/day for adult patients with Ph+ ALL. See section on special populations for pediatric patients.

Dosage in MDS/MPD

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

Dosage in SM

The recommended dose of Glivec is 400 mg/day for adult patients with SM without the D816V KIT mutation or mutational status unknown or not responding satisfactorily to other therapies.

For patients with SM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR-alpha, 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.

Dosage in HES/CEL

The recommended dose of Glivec is 400 mg/day for adult patients with HES/CEL.

For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha fusion kinase, 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.

Dosage in GIST

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

A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

The recommended dose of Glivec is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. The recommended minimum treatment duration is 36 months.

In the adjuvant setting the optimal treatment duration with Glivec is not known.

Dosage in DFSP

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

Dose adjustments for adverse drug reactions

Non-hematological adverse drug reactions

If a severe non-hematological adverse drug reaction develops with Glivec use, treatment must 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, Glivec should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Glivec may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg, or from 600 to 400 mg, or from 800 mg to 600 mg, and in pediatric patients from 340 to 260 mg/m^2/day.

Hematological adverse drug reactions

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

Table 1 Dose adjustments for neutropenia and thrombocytopenia

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Glivec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse drug reaction).
Chronic phase CML, MDS/MPD, SM, HES/CEL and GIST (starting dose 400 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Glivec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse drug 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 Glivec at reduced dose of 300 mg.
Pediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Glivec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse drug 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 Glivec at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	[a]ANC < 0.5 x10^9/L and/or platelets < 10 x10^9/L	1. Check whether cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, reduce dose of Glivec to 400 mg[b]. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d]. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Glivec until ANC ≥ 1 x10^9/L and platelets ≥ 20 x10^9/L, then resume treatment at 300 mg[d].

DFSP (starting dose 800 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Glivec until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Glivec 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 Glivec at reduced dose of 400 mg.

ANC = absolute neutrophil count

[a] occurring after at least 1 month of treatment

[b] or 260 mg/m^2 in pediatric patients

[c] or 340 mg/m^2 in pediatric patients

[d] or 200 mg/m^2 in pediatric patients

Special populations

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis could be given the minimum recommended dose of 400 mg daily as starting dose (see section CLINICAL PHARMACOLOGY) However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment

Imatinib is mainly metabolized by the liver. Patients with mild, moderate or severe liver impairment should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS AND CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

There is no experience with the use of Glivec in pediatric patients with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited to no experience with the use of Glivec in pediatric patients in other indications.

Dosing in pediatric patients should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase CML and Ph+ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening (see section CLINICAL PHARMACOLOGY).

Geriatric patients (65 years or above)

No significant age related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

CONTRAINDICATIONS

Use in patients with a hypersensitivity to the active substance or to any of the excipients is contraindicated.

WARNINGS AND PRECAUTIONS

When Glivec is co-administered with other medications, there is a potential for drug interactions. Caution should be used when taking Glivec with rifampicin or other strong CYP3A4 inducers, ketoconazole or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives) (see section INTERACTIONS).

Hypothyroidism

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

Hepatotoxicity

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections DOSAGE REGIMEN AND ADMINISTRATION, ADVERSE DRUG REACTIONS, CLINICAL PHARMACOLOGY).

When Glivec is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where Glivec is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section ADVERSE DRUG REACTIONS).

Fluid retention

Occurrences of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, and superficial edema) have been reported in approximately 2.5% of newly diagnosed CML patients taking Glivec. Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Patients with cardiac disease or renal failure

Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Glivec therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Glivec. Myelodysplastic (MDS)/myeloproliferative diseases (MPD) and systemic mastocytosis 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 SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with Glivec should be considered at the initiation of therapy.

Gastrointestinal hemorrhage

In the Phase III GIST studies in patients with unresectable or metastatic malignant GIST 211 patients (12.9%) reported Grade 3/4 hemorrhage at any site. In the Phase II GIST study in patients with unresectable or metastatic malignant GIST (study B2222), eight patients (5.4%) were reported to have had gastrointestinal (GI) hemorrhage and four patients (2.7%) were reported to have had hemorrhages at the site of tumor deposits. The tumor hemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumor lesions. GI sites of tumor may have contributed to GI bleeding in this reported patient population. In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI hemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with Glivec. When needed, Glivec discontinuation may be considered (see section ADVERSE DRUG REACTIONS).

Tumor lysis syndrome

Cases of tumor lysis syndrome (TLS) have been reported in patients treated with Glivec. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Glivec (see section ADVERSE DRUG REACTIONS).

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as imatinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section ADVERSE DRUG REACTIONS).

Patients should be tested for hepatitis B infection before initiating treatment with imatinib. Patients currently on imatinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with imatinib should be

closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

Laboratory tests

Haematology

Complete blood counts must be performed regularly during therapy with Glivec. Treatment of CML patients with Glivec has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with Glivec may be interrupted or the dose be reduced, as recommended in section DOSAGE REGIMEN AND ADMINISTRATION.

Liver Function

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Glivec. As recommended in section DOSAGE REGIMEN AND ADMINISTRATION, non-hematological adverse drug reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Glivec.

Renal function

Glivec 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 Glivec kinetics. In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. There is no correlation between imatinib exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCL), between patients with mild (CrCL: 40 to 59 mL/min) and severe (CrCL: <20 mL/min) renal impairment. However, as recommended in section DOSAGE REGIMEN AND ADMINISTRATION, the starting dose of Glivec can be reduced if not tolerated.

Long-term treatment with Glivec may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of Glivec therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be initiated in accordance with standard treatment guidelines.

Pediatric patients (below 18 years)

There have been case reports of growth retardation occurring in children and pre-adolescents receiving Glivec. The long term effects of prolonged treatment with Glivec on growth in pediatric patients are unknown. Therefore, close monitoring of growth in children under Glivec treatment is recommended (see section ADVERSE DRUG REACTIONS).

Driving and using machines

Reports of motor vehicle accidents have been received in patients receiving Glivec. While most of these reports are not suspected to be caused by Glivec, patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Glivec. Therefore, caution should be recommended when driving a car or operating machinery.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The overall safety profile of Glivec in human clinical use has been well-characterized through more than 12 years of Glivec experience. During clinical development, the majority of patients experienced adverse events at some point in time. The most frequently reported ADRs (>10%) were neutropenia, thrombocytopenia, anaemia, headache, dyspepsia, oedema, weight increased, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhoea, rash, fatigue, and abdominal pain. Events were of mild to moderate grade, and only 2 to 5% of patients permanently discontinued therapy due to drug-related events.

The safety profile of Glivec in adult and paediatric patients with Ph+ Leukaemias is similar.

The differences in the safety profile between Ph+ leukaemias and solid tumours are a higher incidence and severity of myelosuppression in Ph+ leukaemias, and GI and intra-tumoural haemorrhages in GIST patients and are probably due to disease-related factors. Myelosuppression, GI adverse events, oedema, and rashes are common between these two patient populations. Other GI conditions, such as gastrointestinal obstruction, perforation and ulceration, appear to be more indication-specific. Other prominent adverse events that have been observed after exposure to Glivec, and which may be causally related, include hepatotoxicity, acute renal failure, hypophosphataemia, severe respiratory adverse reactions, and tumour lysis syndrome and growth retardation in children.

Depending on severity of events, dose adjustment may be required. In very few cases will the medication have to be discontinued based on ADRs.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (Table 2 and Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000). Adverse reactions and their frequencies reported in Table 2 are based on the registration studies for CML and GIST.

Table 2 Adverse drug reactions in clinical studies for CML and GIST

Infections and infestations

Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Blood and lymphatic system disorders	
Very common:	Neutropenia, thrombocytopenia, anaemia
Common:	Pancytopenia, febrile neutropenia
Uncommon:	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare:	Haemolytic anaemia
Metabolism and nutrition disorders	
Common:	Anorexia
Uncommon:	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare:	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
Common:	Insomnia
Uncommon:	Depression, libido decreased, anxiety
Rare:	Confusional state
Nervous system disorders	
Very common:	Headache[2]
Common:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia
Uncommon:	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage
Rare:	Increased intracranial pressure, convulsions, optic neuritis
Eye disorders	
Common:	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon:	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
Rare:	Cataract, glaucoma, papilloedema
Ear and labyrinth disorders	
Uncommon:	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon:	Palpitations, tachycardia, cardiac failure congestive[3], pulmonary oedema
Rare:	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Vascular disorders[4]	
Common:	Flushing, haemorrhage
Uncommon:	Hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud`s phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]

Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage [7], eructation, melena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[9], hepatic necrosis[9]
Skin and subcutaneous tissue disorders	
Very common:	Periorbital edema, dermatitis/eczema/rash
Common:	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very common:	Muscle spasm and cramps, Musculoskeletal pain including myalgia, arthralgia, bone pain[8]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis
Renal and urinary disorders	
Uncommon:	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased
Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

[1] Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.

[2] Headache was the most common in GIST patients.

[3] On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.

[4] Flushing was most common in GIST patients and bleeding (hematoma, hemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).

[5] Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.

[6/7] Abdominal pain and gastrointestinal hemorrhage were most commonly observed in GIST patients.

[8] Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.

[9] Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

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

Table 3 Adverse drug reactions from post-marketing reports

Infections and infestations		
	Not known:	Hepatitis B reactivation
Nervous system disorders		
	Uncommon:	Cerebral oedema
Eye disorders		
	Rare:	Vitreous haemorrhage
Cardiac disorders		
	Rare:	Pericarditis, cardiac tamponade
Vascular disorders		
	Uncommon:	Thrombosis/embolism
	Very rare:	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders		
	Uncommon:	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation[2]
	Rare:	Diverticulitis, gastric antral vascular ectasia (GAVE)
Skin and subcutaneous tissue disorders		
	Uncommon:	Palmar-plantar erythrodysaesthesia syndrome, panniculitis (including erythema nodosum)
	Rare:	Lichenoid keratosis, lichen planus, pemphigus
	Very rare:	Toxic epidermal necrolysis
	Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria
Musculoskeletal and connective tissue disorders		
	Very common:	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)
	Uncommon:	Osteonecrosis
	Rare:	Rhabdomyolysis/myopathy
	Not known:	Growth retardation in children
Reproductive disorders		
	Very rare:	Haemorrhagic corpus luteum / haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)		
	Rare:	Tumour lysis syndrome

[1] Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions

[2] Some fatal cases of gastrointestinal perforation have been reported

Description of selected adverse drug reactions

Myelosuppression

Myelosuppression is very common in cancer patients treated with Glivec. Myelosuppression, thrombocytopenia, neutropenia and anaemia were the most frequently reported Grade 3 and 4 laboratory abnormalities. Overall, myelosuppression experienced with Glivec in CML patients was generally reversible and in most patients did not result in dose interruption or dose reduction. Few patients required drug discontinuation. Other events of pancytopenia, lymphopenia and bone marrow depression have also been reported.

Haematologic depression appeared greatest at the highest doses and also appeared to be dependent on the stage of CML disease, with Grade 3 or 4 neutropenia and thrombocytopenia between 4 and 6 times higher in blast and accelerated phase (44% and 63%, respectively) as compared to newly diagnosed patients in CP CML (16.7% and 8.9%, respectively). These events can usually be managed with either a dose reduction or interruption , but they rarely require discontinuation of treatment with Glivec. The incidence of hematologic toxicities is less in patients with solid tumours (i.e. GIST) than in patients with Ph+ leukaemias, with Grade 3/4 neutropenia and thrombocytopenia occurring approximately 10% and 1%, respectively.

Haemorrhage

CNS and GI haemorrhages are not uncommon in CML patients with compromised marrow function at baseline. Haemorrhages are well-recognized part of the disease complications in an acutely ill population of leukaemic patients, and may result from thrombocytopenia, or less commonly, platelet dysfunction. However, not all patients experiencing CNS and GI haemorrhages during therapy with imatinib are thrombocytopenic.

The most common manifestation of clinically significant bleeding was GI haemorrhage, which occurred most commonly in advanced CML patients and in metastatic GIST patients, where bleeding might occur as part of the underlying disease due to tumour bleeding from tumour haemorrhage/tumour necrosis. In first line CML and in adjuvant GIST setting, the observed frequencies of GI haemorrhage were generally the lowest. Gastric antral vascular ectasia (GAVE) is also rarely reported with Glivec use in the post-marketing setting.

Oedema and Fluid Retention

Oedema is a common toxicity of imatinib appearing in greater than 50% of all patients across all indications. Oedema is dose-related and there appears to be a correlation with its occurrence and plasma levels. The most common manifestation is periorbital oedema and somewhat less common is lower extremity oedema. Specific therapy is not usually required. Other fluid retention events occur much less commonly, but due to the location of the anatomic site may be potentially serious. The most frequent fluid retention event was pleural effusion, most commonly observed in advanced CML and metastatic GIST patients. The frequency of cardiac

failure was generally low in patients with oedema and fluid retention. It was higher in advanced CML than in other groups. This could be explained by the worse medical condition of advanced CML patients. The same trend was observed for renal failure in patients with oedema and fluid retention.

In a clinical study, the frequency of events suggesting congestive heart failure was 1.5% on imatinib vs. 1.1% on IFN-alpha in patients with newly-diagnosed CML. The frequency was appreciably higher in patients with transformed CML (accelerated phase or blast crisis), higher age, or with a baseline haemoglobin of less than 8 g/dL. Congestive Heart Failure (CHF) and left ventricular dysfunction have since been continuously monitored in the PSUR. Across all indications a higher frequency of CHF events observed in patients with CML than in patients with GIST might indicate differences of some of these disease-related risk factors. In addition, a recently published special safety analysis of cardiac events within the EORTC study of 942 patients with unresectable or metastatic GIST concluded that imatinib does not induce left ventricular failure in GIST patients where the observed rate was approximately 0.2% while it can be up to 2% in a population with pre-existing cardiac disease.

Skin Rashes and Severe Cutaneous Adverse Reactions

A generalized erythematous, maculopapular, pruritic skin rash has been reported that can fade despite continued therapy. Some patients may have pruritus without accompanying rash, and sometimes there is an exfoliative component. Re-exposure in some patients has resulted in reappearance of rash, but not in all patients. These eruptions generally respond to antihistamines and topical steroids. Occasionally, systemic steroids are required.

Skin rashes have been observed in up to one third of patients treated with imatinib across all indications. These are frequently pruritic and most commonly appear as erythematous, maculopapular or exfoliative lesions on the forearm, the trunk or the face or generalized with systemic expression. Skin biopsies have revealed a toxic drug reaction with a mixed cellular infiltrate. Although most rashes are mild and self-limiting more severe rare cases such as Stevens-Johnson toxic epidermal necrolysis, Erythema multiforme or DRESS may require interruption or discontinuation of treatment. Not surprisingly skin reactions were seen at a higher rate than placebo in the adjuvant GIST trial.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur, and has been observed preclinically and clinically. LFT abnormalities usually consisted of mild elevations in transaminases, although a minority of patients had elevated levels of bilirubin. Onset is generally within the first two months of therapy, but has occurred as late as 6 to 12 months after commencing therapy. The levels generally normalize after withholding therapy for 1 to 4 weeks.

Hypophosphataemia

Low serum phosphate and hypophosphataemia (up to Grade 3 or 4) has been observed relatively commonly across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive

capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of imatinib. Sustained inhibition of osteoclastic activity may lead to counter regulatory response resulting in increased levels of PTH. The clinical relevance of the preclinical findings is yet unclear and an association with skeletal AEs such as bone fractures has not been demonstrated.

In the clinical development program serum phosphate was not routinely measured in all studies. Although it was initially hypothesized that hypophosphataemia might be dose-dependent, 24 month interpretable results from the Phase III TOPS study designed to investigate dose dependency of safety endpoints in patients with newly diagnosed CML, have shown that Grade 3 or 4 decreased serum phosphate or serum calcium has been experienced by 19.1% vs.15.5% and 5.1% vs. 0.9% of patients receiving 400 mg and 800 mg, respectively.

Gastrointestinal Obstruction, Perforation or Ulceration

GI ulceration, which may represent in extreme cases local irritation by imatinib, has been observed in a small proportion of patients across all indications. Tumour haemorrhage/tumour necrosis, obstruction and GI perforation seem to be disease-related and have occurred exclusively or more frequently amongst GIST patients. In the case of metastatic GIST, tumor necrosis may occur in the context of tumor response, rarely leading to perforation. GI obstruction/ileus occurred most commonly in the GIST population where it may be caused by tumor obstruction from metastatic GIST and in the adjuvant setting by adhesions from previous GI surgery.

Tumour lysis syndrome

A causal relationship between tumour lysis syndrome and Glivec treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks (see section WARNINGS AND PRECAUTIONS).

Growth retardation in pediatric patients

Glivec appears to affect the stature of children, especially children who are pre-pubertal. A causal relationship between growth retardation in pediatric patients and Glivec treatment could not be ruled out although for some cases of growth retardation in CML there was limited information (see section WARNINGS AND PRECAUTIONS).

Severe respiratory adverse drug reaction

Severe respiratory events, sometimes fatal, have been observed with Glivec treatment, including acute respiratory failure, pulmonary hypertension, interstitial lung disease and pulmonary fibrosis. Pre-existing cardiac or pulmonary conditions that may be associated with severe respiratory events have been reported in many of these cases.

Laboratory test abnormalities

Haematology

CML-associated cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high 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 the other CML patients. The frequency of Grade 3 or 4 neutropenias (ANC $<1.0x10^9$/L) and thrombocytopenias (platelet count $<50x10^9$/L) being between 4 and 6 times higher in blast crisis and accelerated phase (59 to 64% and 44 to 63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). In newly diagnosed chronic phase CML Grade 4 neutropenia (ANC $<0.5x10^9$/L) and thrombocytopenia (platelet count $<10x10^9$/L) were observed in 3.6% and <1 % of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a dose reduction or an interruption of treatment with Glivec, but can in rare cases lead to permanent discontinuation of treatment. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

In patients with unresectable or metastatic malignant GIST (study B2222), Grade 3 and 4 anaemias were reported in 5.4% and 0.7% of patients, respectively, and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia were seen in 7.5% and 2.7% of patients, respectively, and Grade 3 thrombocytopenia in 0.7% of patients. No patient developed Grade 4 thrombocytopenia. The decreases in WBC and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

Biochemistry

Severe elevation of transaminases (<5%) or bilirubin (<1%) has been seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week) of Glivec. Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of Grade 3 or 4 SGPT (serum glutamic pyruvic transferase) elevations and 4.8% of Grade 3 or 4 SGOT (serum glutamic oxaloacetic transferase) elevations were observed. Bilirubin elevation was below 3%.

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

INTERACTIONS

Observed interactions resulting in a concomitant use not recommended

Drugs that may decrease imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Glivec. Pretreatment of 14 healthy volunteers with multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of Glivec, increased Glivec oral-dose clearance by 3.8 fold (90% confidence interval = 3.5 to 4.3 fold), which represents mean decreases C_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with Glivec while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. In two published studies, concomitant administration of Glivec and a product containing St. John's wort led to a 30 to 32% reduction in the AUC of Glivec. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Other interactions that may affect exposure to Glivec or other drugs

Drugs that may increase imatinib plasma concentrations

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

Drugs that may have their plasma concentration altered by Glivec

Glivec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2 and 3.5 fold, respectively, indicating an inhibition of the CYP3A4 by Glivec. Therefore, caution is recommended when administering Glivec with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Glivec may increase plasma concentration of other CYP3A4 metabolized drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

Glivec also inhibits CYP2C9 and CYP2C19 activity *in vitro*. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of Glivec therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.

In vitro, Glivec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Glivec at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23%. Co-administration of Glivec with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.

In vitro, Glivec inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 microM).

Co-administration of Glivec (400 mg/day for eight days) with acetaminophen/paracetamol (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen/paracetamol.

Glivec pharmacokinetics was not altered in the presence of single-dose acetaminophen/ paracetamol.

There is no PK or safety data on the concomitant use of Glivec at doses >400 mg/day or the chronic use of concomitant acetaminophen/paracetamol and Glivec.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Glivec can cause fetal harm when administered to a pregnant woman based on findings from animal reproduction studies. There are no clinical trials on the use of Glivec in pregnant women. There have been postmarketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Glivec. Reproductive studies in rats have demonstrated that imatinib mesylate induced teratogenicity (increased incidence of congenital abnormalities) following prenatal exposure to imatinib mesylate at doses equal to the highest recommended human dose of 800 mg/day based on body surface area. Glivec should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.

Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of imatinib mesylate up to 100 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, imatinib mesylate was teratogenic at 100 mg/kg/day (approximately equal to the maximum human dose of 800 mg/day based on body surface area), the number of fetuses with encephalocoele and exencephaly was higher than historical control values and these findings were associated with missing or underdeveloped cranial bones. Lower mean fetal body weights were associated with retarded skeletal ossifications.

In rabbits, at doses 1.5 times higher than the maximum human dose of 800 mg/day based on body surface area, no effects on the reproductive parameters with respect to implantation sites, number of live fetuses, sex ratio or fetal weight were observed. The examinations of the fetuses did not reveal any drug related morphological changes.

In a pre- and postnatal development study in rats, pregnant rats received oral doses of imatinib mesylate during gestation (organogenesis) and lactation up to 45 mg/kg/day. Five animals developed a red vaginal discharge in the 45 mg/kg/day group on Days 14 or 15 of gestation, the significance of which is unknown since all females produced viable litters and none had increased post-implantation loss. Other maternal effects noted only at the dose of 45 mg/kg/day (approximately one-half the maximum human dose of 800 mg/day based on body surface area) included increased numbers of stillborn pups and pups dying between postpartum Days 0 and 4. In the F1 offspring at this 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. There were no other significant effects in developmental parameters or behavioral testing. F1 fertility was not affected but reproductive effects were noted at 45 mg/kg/day including an increased number of resorptions and a decreased number of viable fetuses. The NOEL for both maternal animals and the F1 generation was 15 mg/kg/day.

Lactation

Risk summary

Both imatinib and its active metabolite can be transferred into human milk. The effects of low-dose exposure of the infant to imatinib are unknown, because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 15 days after stopping treatment with Glivec.

Human Data

The milk plasma ratio was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and of the metabolite and the maximum daily milk intake by infants the total exposure would be expected to be approximately ~10% of a therapeutic dose.

Females and males of reproductive potential

Females

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

Infertility

Human studies on male patients receiving Glivec and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on

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

OVERDOSAGE

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

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

Adult overdose

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

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

Pediatric overdose

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the BCR-ABL tyrosine kinase (TK), as well as several receptor TKs: KIT, the receptor for stem cell factor (SCF) coded for by the KIT proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

Pharmacodynamics (PD)

Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase at the *in vitro*, cellular, *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 CML and acute lymphoblastic leukemia (ALL) patients. In colony transformation assays using ex *vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients.

In vivo the compound shows anti-tumor activity as a single agent in animal models using BCR-ABL positive tumor cells.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), 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 MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of 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.

Pharmacokinetics (PK)

The pharmacokinetics of Glivec have been evaluated over a dosage range of 25 to 1,000 mg. Plasma pharmacokinetic profiles were analyzed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

Absorption

Mean absolute bioavailability for the capsule formulation imatinib is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40% to 60% after an oral dose. When given with a high fat meal, the rate of absorption of imatinib was minimally 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 was approximately 95% on the basis of *in vitro* experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

Biotransformation/metabolism

The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP71588), which shows similar *in vitro* potency as the parent compound. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Elimination

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.

The mean apparent elimination half-life estimated from the single dose PK study was 13.5 hours. The half-life of all ^{14}C-labelled components in plasma was from 41-72 hours.

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the $t_{½}$ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 to 1,000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5 to 2.5 fold at steady state when dosed once daily.

Special populations

Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12% increase in patients >65 years old). This change is not thought to be clinically significant. 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 kg bodyweight. There is no effect of gender on the kinetics of imatinib.

Further population PK analysis in the phase III study in newly diagnosed CML patients showed that the effect of covariates and co-medications on both clearance and volume of distribution appears to be small and is not sufficiently pronounced to warrant dose adjustment.

Pediatric patients (below 18 years)

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/m^2 achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on Day 8 and Day 1 at 340 mg/m^2 dose level revealed a 1.7 fold drug accumulation after repeated once daily dosing.

Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 260 mg/m2 once daily (not exceeding 400 mg once daily) or 340 mg/m2 once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

Organ function impairment

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2 fold, corresponding to a 1.5 fold elevation of plasma AGP, to which imatinib binds strongly. The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib (see sections DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY - Pharmacodynamics).

Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function (see sections DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS, CLINICAL PHARMACOLOGY - Pharmacodynamics and Pharmacokinetics).

CLINICAL STUDIES

Clinical studies in CML

The effectiveness of Glivec is based on overall hematological and cytogenetic response rates and progression free survival.

Three large, international, open-label, non-controlled phase II studies were conducted in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in advanced, blast or accelerated phase disease, other Ph+ leukemias or with CML in the chronic phase but failing prior interferon-alpha (IFN) therapy. One large, open-label, multicenter, international randomized phase III study has been conducted in patients with newly diagnosed Ph+ CML. In addition, children have been treated in two phase I studies and one open-label, multicenter, single arm phase II trial.

In all clinical studies 38 to 40% of patients were ≥60 years of age and 10 to 12% of patients were ≥70 years of age.

Chronic phase, newly diagnosed: This phase III study compared treatment with either single-agent Glivec at 400mg daily or a combination of 5 MIU/m^2/day IFN and 20 mg/m^2/day Ara-C, both subcutaneously for 10 days/month. Patients showing lack of response (lack of complete hematological response (CHR) at 6 months, increasing white blood cells (WBC), no major cytogenetic response (MCyR) at 24 months), loss of response (loss of CHR or McyR) or severe intolerance to treatment were allowed to crossover to the alternative treatment arm. A total of 1,106 patients were randomized, 553 to each arm. Median age was 51 years (range 18 to 70 years), with 21.9% of patients ≥60 years of age. 59% males and 41% females; At the 7 year follow-up,, the median duration of first-line treatment was 82 and 8 months in the Glivec and IFN arm, respectively. The median duration of second-line treatment with Glivec was 64 months. Overall, in patients receiving first line Glivec, the average daily dose delivered was 406±76 mg. As a consequence of a higher rate of both discontinuations and crossovers, only

2% of patients randomized to IFN are still on first line treatment. In the IFN arm, withdrawal of consent (14%) was the most frequent reason for discontinuation of first line therapy, and the most frequent reason for crossover to the Glivec arm was severe intolerance to treatment (26%) and progression (14%). The primary efficacy endpoint of the study is progression-free survival. Progression was defined as any of the following event: progression to accelerated phase or blast crisis (AP/BC), death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. Major cytogenetic response, hematological response, molecular response (evaluation of minimal residual disease), time to accelerated phase or blast crisis and survival are main secondary endpoints. Response data are shown in Table 4.

Table 4 Response in newly diagnosed CML Study (84-month data)

	Glivec	**IFN+Ara-C**
(Best response rates)	n=553	n=553
Hematological response		
CHR rate - n (%)	534 (96.6)*	313 (56.6)*
[95 % CI]	[94.7, 97.9]	[52.4, 60.8]
Cytogenetic response		
Major response - n (%)	490 (88.6)	129 (23.3)
[95 % CI]	[85.7, 91.1]	[19.9, 27.1]
Complete CyR -n (%)	456 (82.5)	64 (11.6)
Partial CyR -n (%)	34 (6.1)	65 (11.8)
Molecular response		
Major response at 12 months (%)	40*	2*
Major response at 24 months (%)	54	NA**

* $p < 0.001$, Fischer's exact test

**insufficient data, only two patients available with samples

Hematological response criteria (all responses to be confirmed after ≥4 weeks):

WBC < 10 x10^9/L, platelet < 450 x10^9/L, myelocyte+metamyelocyte < 5 % in blood, no blasts and promyelocytes in blood, basophils < 20 %, no extramedullary involvement

Cytogenetic response criteria: complete (0 % Ph+ metaphases), partial (1-35 %), minor (36-65 %) or minimal (66-95 %). A major response (0-35 %) combines both complete and partial responses.

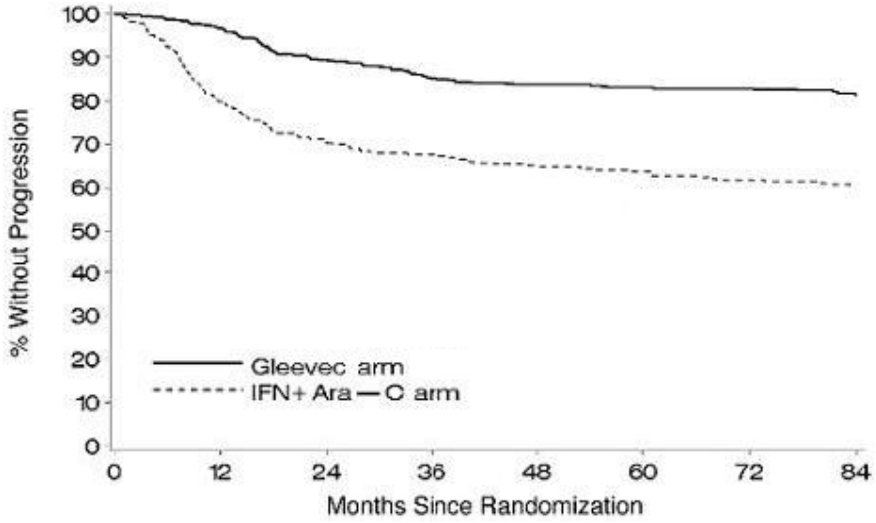
Major molecular response criteria: in the peripheral blood, reduction ≥3 logarithms in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline.

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

The estimated rate of progression-free survival at 84 months is 81.2% with 95% CI (78, 85) in the Glivec arm and 60.6% (56, 5) in the control arm ($p < 0.001$) (Figure 1). The yearly rates of progression for Glivec were 3.3% in the 1st year after start of study, 7.5% in the 2nd year and 4.8%, 1.7%, 0.8% 0.3% and 2.0% in the 3rd, 4th, 5th, 6th and 7th year of study respectively.

The estimated rate of patients free of progression to accelerated phase or blast crisis at 84 months was significantly higher in the Glivec arm compared to the IFN arm (92.5% versus 85.1%, p<0.001).

Figure 1 Time to progression (ITT principle)



A total of 71 (12.8%) and 85 (15.4%) patients died in the Glivec and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80, 87) in the randomized Glivec and the IFN+Ara-C groups, respectively (p=0.073, log-rank test). This time-to-event endpoint is strongly affected by the high crossover rate from IFN+Ara-C to Glivec. When censoring the 48 deaths that occurred after BMT, the 84-months survival rates were 89.6 vs 88.1 (p=0.200, log-rank test). Only 31 deaths (before BMT) of the Glivec patients (5.6%) were attributed to CML, compared to 40 of the IFN+Ara-C patients (7.2%). When only considering these CML-related deaths and censoring any deaths after BMT or due to other reasons, the estimated 84-months survival rates were 93.6% vs. 91.1% (p=0.1, log rank test). In this study, dose escalations 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, 11 patients who achieved a CHR at 3 months and a MCyR at 12 months while on a daily dose of 400 mg experienced a confirmed loss (within 4 weeks) of their cytogenetic response. Of these 11 patients, 4 patients escalated up to 800 mg daily, 2 of whom regained a cytogenetic response (1 partial and 1 complete, the latter also achieving a molecular response), while of the 7 patients in whom the dose was not escalated, only one regained a complete cytogenetic response. The percentage of some ADRs was 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 ADRs included gastrointestinal hemorrhages, conjunctivitis and elevation of transaminases or bilirubin. Other ADRs were reported with lower or equal frequency.

Chronic phase, Interferon-failure: 532 patients were treated at a starting dose of 400 mg. The patients were distributed in three main categories: hematological 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).

In this study, 65% of the patients achieved a MCyR, which was complete in 53% of patients CHR was achieved in 95% of patients.

Accelerated phase: 235 patients with accelerated phase disease were enrolled. The first 77 patients were started at 400 mg, and the remaining 158 patients were started at 600 mg.

The primary efficacy variable was the rate of hematological response, reported as either CHR, 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. A confirmed hematological response was achieved in 71.5% of patients. Importantly, 27.7% of patients also achieved a MCyR, which was complete in 20.4% of patients. For the patients treated at 600 mg, the current estimates for median progression-free survival and overall survival were 22.9 and 42.5 months, respectively. In a multivariate analysis, a dose of 600 mg was associated with an improved time to progression, independent of platelet count, blood blasts and hemoglobin ≥10 g/L.

Myeloid blast crisis: 260 patients with myeloid blast crisis were enrolled. 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pre-treated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg, and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the rate of hematological response, reported as either CHR, no evidence of leukemia, or return to chronic phase CML 31% of patients achieved a hematological response (36% in previously untreated patients and 22% in previously treated patients). The rate of response was also higher in the patients treated at 600 mg (33%) as compared to the patients treated at 400 mg (16%, p=0.0220). The current estimate of the median survival of the previously untreated and treated patients was 7.7 and 4.7 months, respectively.

Pediatric patients: A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase II trial, and were treated with Glivec 340 mg/m^2/day. Glivec treatment induced a rapid response in newly diagnosed pediatric CML patients with a CHR of 78% after 8 weeks of therapy and a complete cytogenetic response (CCyR) of 65% (comparable to results in adults) after 3 to 10 months of treatment.

A total of 31 heavily pre-treated pediatric patients (45 % with prior BMT and 68% with prior multi-agent chemotherapy) with either chronic phase CML (n=15) or CML in blast crisis or Ph+ ALL (n=16) were enrolled in a dose escalation phase I trial. Patients were treated at doses of Glivec ranging between 260 mg/m^2/day and 570 mg/m^2/day. Out of 13 patients with CML and cytogenetic data available, 7 (54%) and 4 (31%) achieved a complete and partial cytogenetic response, respectively, for a rate of MCyR of 85%.

Clinical studies in Ph+ ALL

A total of 851 Ph+ ALL patients with either newly diagnosed or relapsed/refractory disease were enrolled in eleven clinical studies, ten of which were uncontrolled and one was randomized. Of the 851 patients, 93 were pediatric patients (including 4 patients older than 18 and younger than 22 years) treated in one open-label, multicenter, non-randomized phase III study.

Newly diagnosed Ph+ ALL

In a controlled study (ADE10) of Glivec versus chemotherapy induction in 55 newly diagnosed patients aged 55 years and over, Glivec used as single agent induced a significantly higher rate of complete hematological response than chemotherapy (96.3% vs. 50%; p=0.0001). When salvage therapy with Glivec was administered in patients who did not respond or who responded poorly to chemotherapy, it resulted in 9 patients (81.8%) out of 11 achieving a complete hematological response. This clinical effect was associated with a higher reduction in BCR-ABL transcripts in the Glivec-treated patients than in the chemotherapy arm after 2 weeks of therapy (p=0.02). All patients received Glivec and consolidation chemotherapy after induction and the levels of BCR-ABL transcripts were identical in the two arms at 8 weeks. As expected on the basis of the study design, no difference was observed in remission duration, disease-free survival or overall survival, although patients with complete molecular response and remaining in minimal residual disease had a better outcome in terms of both remission duration (p=0.01) and disease-free survival (p=0.02).

The results observed in a population of 211 newly diagnosed Ph+ ALL patients in four uncontrolled clinical studies (AAU02, ADE04, AJP01 and AUS01) are consistent with the results described above, Similarly, in two uncontrolled clinical studies (AFR09 and AIT04) 49 newly diagnosed Ph+ ALL patients aged 55 years and over were given Glivec combined with steroids with or without chemotherapy Results are shown in Table 5.

Table 5 Effect of Glivec in newly diagnosed Ph+ ALL adult patients

Study	AAU02	ADE04	AJP01	AUS01	AFR09	AIT04	ADE10§	
	Glivec and CHT	Glivec and CHT	Glivec and CHT	Glivec and CHT	Glivec and CHT/ steroids	Glivec and steroids	Glivec	CHT
		Cohort 2						
N (evaluable for CHR)	12	45	80	21	29	18	27	26
CHR (%)	58	95	96	95	72	100	96	50*
95% C.I.	28 - 85	85 - 99	89 - 99	76 - 100	53 - 87	82 - 100	81 - 100	30 - 70
CHR Historical controls [CHT]			51 (p<0.0001)	61 – 94 (p<0.01)	29 (p=0.003)			
N (overall)	24	47	80	20	30	19	28	27
1-year DFS (%)	NA	NA	61 ± 6	87	60	-	54	
Median DFS (m)	-	-	-	-	-	15	-	
1-year OS (%)	61 ± 13&	NA	76 ± 5	-	68	-	54	
2-year OS (%)	-	NA	-	75**	-	-	-	

Study	AAU02	ADE04	AJP01	AUS01	AFR09	AIT04	ADE10§
Median OS (m)	-	-	-	-	-	20	-

CHR = complete hematological response
CHT = chemotherapy
m = months
NA = Not available
* p<0.01
§ after induction
** on the first 20 patients both newly diagnosed and relapse/refractory
& on all patients, including newly diagnosed, relapsed patients and CML blastic crisis

Pediatric patients: In study I2301, a total of 93 pediatric, adolescent and young adult patients (including 4 patients older than 18 and younger than 22 years) with Ph+ ALL were enrolled in an open-label, multicenter, sequential cohort, non-randomized phase III trial, and were treated with Glivec (340 mg/m^2/day) in combination with intensive chemotherapy after induction therapy. Glivec was administered intermittently in cohorts 1 to 5, with increasing duration and earlier start of Glivec from cohort to cohort; cohort 1 receiving the lowest intensity and cohort 5 receiving the highest intensity of Glivec (longest duration in days with continuous daily Glivec dosing during the first chemotherapy treatment courses). Continuous daily exposure to Glivec early in the course of treatment in combination with chemotherapy in cohort 5 patients (n=50) improved the 4-year event-free survival (EFS) compared to historical controls (n=120), who received standard chemotherapy without Glivec (69.6% vs. 31.6%, respectively). The estimated 4-year OS in Cohort 5 patients was 83.6% compared to 44.8% in the historical controls.

Relapsed/refractory Ph+ ALL

When Glivec was used as single agent in patients with relapsed/refractory Ph+ ALL, it resulted, in the 66 out of 429 patients evaluable for response, in a hematological response rate of 33% (12% complete) and a major cytogenetic response rate of 23%. The median time to progression in the overall population of 429 patients with relapsed/refractory Ph+ ALL ranged from 1.9 to 3.1 months, and median overall survival in the 409 evaluable patients ranged from 5 to 9 months. In 14 patients, Glivec in combination with induction chemotherapy resulted in a complete hematological response rate of 92% in 12 evaluable patients and a major cytogenetic response rate of 100% in 8 evaluable patients. Molecular response was assessed in four patients, and two responded completely.

A total of 14 out of 146 patients were treated with Glivec 600 mg daily and were evaluable for response; complete hematological response was observed in 5 patients (35%) and major cytogenetic response in 7 patients (50%). Of note, four patients who were treated with a lower dose of Glivec (400 mg daily) did not respond. In the overall population of 146 patients, median disease-free survival ranged from 2.8 to 3.1 months and median overall survival from 7.4 to 8.9 months.

Clinical studies in MDS/MPD

One open label, multicenter, phase II clinical trial (study B2225) was conducted testing Glivec 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 out of a total of 185 patients treated, 45 of whom had hematological diseases and 140 a variety of solid tumors. These patients were treated with Glivec 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 Glivec at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 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 responded hematologically (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 hematological response and one (6%) achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8 to 26.7) in the 7 patients treated within study B2225 and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 6.

Table 6 Response in MDS/MPD

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

NE: Not evaluable

Clinical studies in SM

This study B2225 also included 5 patients (aged 49 to 74) with SM, receiving Glivec 100 mg to 400 mg daily A further 25 patients receiving Glivec at doses of 100 mg to 400 mg daily, with SM (aged 26 to 85 years) were reported (10 published case reports and case series). Of the total of 30 SM patients, 10 (33%) achieved a complete hematological response and 9 (30%) a partial hematological response (63% overall response rate). Cytogenetic abnormalities were evaluated in 21 of 30 patients treated in the published reports and study B2225. Eight out of 21 patients

had a FIP1L1-PDGFR-alpha fusion kinase, which is typically in males with or without eosinophilia. Two patients showed a KIT mutation in the juxta membrane region (one Phe522Cys and one K509I). Sixteen patients had unknown or no detected cytogenetic abnormality. Four patients showed a D816V mutation (the one responder had concomitant CML and SM). The majority of patients in literature with the D816V KIT mutation are not considered sensitive to Glivec. Median duration of therapy was 13 months (range 1.4 to 22.3 months) in 5 patients in study B2225 and ranged between 1 and more than 30 months in responding patients in the literature. Results are provided in Table 7.

Table 7 Response in SM

Cytogenetic abnormality	Number of patients	Complete hematological response	Partial hematological response
FIP1L1-PDGFR-alpha fusion kinase (or CHIC2 deletion)	8	8	0
Juxta membrane mutation	2	0	2
Unknown or no cytogenetic abnormality detected	16	1	7
D816V mutation	4	1*	0
Overall totals	30	10 (33%)	9 (30%)

*Patient had concomitant CML and SM

Clinical studies in HES/CEL

This study, B2225 also included 14 patients (aged 16 to 64) with HES/CEL receiving Glivec 100 mg to 1,000 mg daily. A further 162 patients receiving Glivec at doses of 75 mg to 800 mg daily, with HES/CEL (aged 11 to 78 years) were reported (35 published case reports and case series). Of the population of 176 patients treated for HES/CEL, 107 (61%) achieved a complete hematological response and 16 (9%) a partial hematological response (70% overall response rate). Cytogenetic abnormalities were evaluated in 117 of 176 patients treated in the published reports and in study B2225. FIP1L1-PDGFR-alpha fusion kinase was found in 61 of 117 patients. All of these FIP1L1-PDGFR-alpha fusion kinase positive patients achieved a complete hematological response. The FIP1L1-PDGFR-alpha fusion kinase was either negative or unknown in 115 patients, of which 62 (54%) achieved either a complete (n=46) or partial (n=16) hematological response. Results are provided in Table 8.

Table 8 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematological response	Partial hematological response
Positive FIP1L1-PDGFR-alpha fusion kinase	61	61	0
Negative FIP1L1-PDGFR-alpha fusion kinase	56	12	9
Unknown cytogenetic abnormality	59	34	7
Overall totals	176	107 (61%)	16 (9%)

Additionally, improvements in symptomatology and organ dysfunction abnormalities (cardiac, nervous, skin/subcutaneous tissue, respiratory/thoracic/mediastinal, musculoskeletal/connective tissue/vascular, and gastrointestinal organ system) were reported in the case reports.

Clinical studies in unresectable or metastatic GIST

Two open-label, randomized, multinational Phase III studies (SWOG, EORTC) were conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). A total of 1,640 patients were randomized 1:1 to receive either 400 mg or 800 mg orally q.d. continuously until disease progression or unacceptable toxicity. Crossover was permitted to 800 mg q.d. The studies were designed to compare response rates, progression free survival and overall survival between the dose groups. All patients had a pathologic diagnosis of CD117 positive unresectable and/or metastatic malignant GIST.

The primary objective of the two studies was to evaluate either progression free survival (PFS) with a secondary objective of overall survival (OS) in one study (EORTC) or overall survival with a secondary objective of PFS in the other study (SWOG). A planned analysis of both OS and PFS from the combined datasets from these two studies was conducted. Results from this combined analysis are shown in Table 9.

Table 9 Overall survival, Progression Free Survival and Tumor Response Rates in the Phase III GIST Trials

	Glivec 400 mg N=818	Glivec 800 mg N=822	Total N=1640
Progression Free Survival (months)			
(50% median)	18.9	23.2	21.0
[95% CI]	[17.4-21.2]	[20.8-24.9]	[19.4-22.5]
Overall Survival (months)	49.0	48.7	48.8
[95% CI]	[45.3-60.0]	[45.3-51.6]	[46.3-51.6]
Best Overall Tumor Response			
Complete Response (CR)	43 (5.3%)	41 (5.0%)	84 (5.1%)
Partial Response (PR)	377 (46.1%)	402 (48.9%)	779 (47.5%)
Not Confirmed (NC)*	235 (28.7%)	224 (27.3%)	459 (28.0%)
Progressive Disease	103 (12.6%)	78 (9.5%)	181 (11.0%)
Missing	60 (7.3%)	77 (9.4%)	137 (8.4%)

*NC includes patients with unconfirmed responses, no change and lack of progressive disease

Median follow up for the combined studies was 37.5 months). There was a statistically significant improvement in PFS in the 800 mg treatment group (23.2 vs. 18.9 months in the 400 mg arm (p=0.03). However, there were no observed differences in OS between the treatment groups (p=0.98). The estimated overall PFS for all 1640 patients in these Phase III studies was 21 months and the estimated OS was 48.8 months. Only 5.1% of patients achieved a confirmed complete response and 47.5% achieved a partial response. Treatment at either dose level was generally well tolerated and overall 5.4% of patients withdrew due to toxicity.

One phase II, open-label, randomized multinational study was conducted in patients with unresectable or metastatic GIST. In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally once daily for up to 36 months.

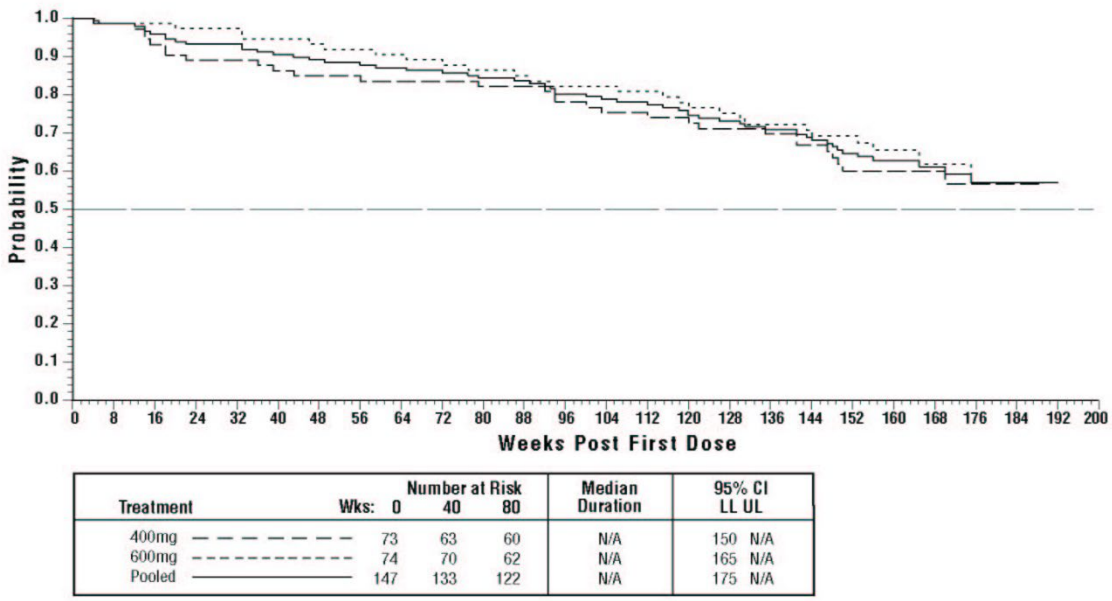
The primary evidence of efficacy was based on objective response rates. Response characterization was based on Southwestern Oncology Group (SWOG) criteria. In this study, 83% of the patients achieved either a complete response, partial response or stable disease. Results are provided in Table 10.

Table 10 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)

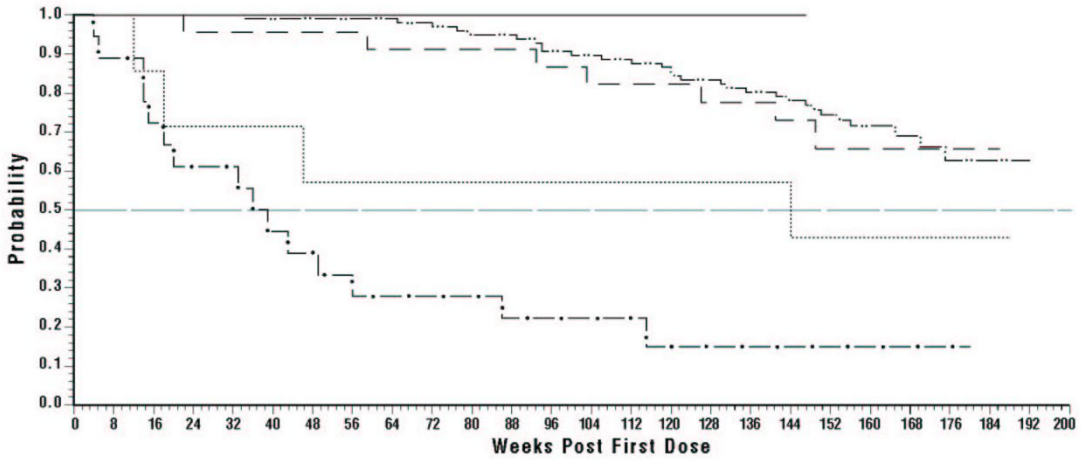
There were no differences in response rates between the two dose groups (median follow-up 31 months). Median time to response was 13 weeks. Median time to treatment failure in responders was 122 weeks, while in the overall study population it was 84 weeks. The median overall survival has not been reached. The Kaplan-Meier estimate for survival after 36-month follow-up is 68% (Figure 2). Additionally, there is no difference in survival between patients achieving stable disease and partial response (Figure 3).

Figure 2 Kaplan-Meier estimate of overall survival since start of study by treatment



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

Figure 3 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

Clinical studies in adjuvant GIST

In the adjuvant setting, Glivec was investigated in a multicenter, double-blind, long-term, placebo controlled phase III study (Z9001) involving 713 patients. The primary endpoint of the study was recurrence free survival (RFS) defined as the time from date of randomization to the date of recurrence or death from any cause.

Glivec prolonged significantly RFS with 75% of patients being recurrence-free at 38 months in the Glivec group vs 20 months in the placebo group (95% CIs, [30 non-estimable]; [14 non-estimable], respectively); (hazard ratio = 0.398 [0.259 to 0.610], p<0.0001). At one year the overall RFS was significantly better for Glivec (97.7%) vs. placebo (82.3%), (p<0.0001) therefore reducing the risk of recurrence by approximately 89% as compared with placebo (hazard ratio = 0.113 [0.049 to 0.264]).

A second open label phase III study (SSG XVIII/AIO) compared 400 mg/day Glivec 12 months treatment vs. 36 months treatment in patients after surgical resection of GIST and one of the following: tumor diameter >5 cm and mitotic count >5/50 high power fields (HPF); or tumor diameter >10 cm and any mitotic count or tumor of any size with mitotic count >10/50 HPF or tumors ruptured into the peritoneal cavity. There were a total of 397 patients consented and randomized to the study (199 patients on 12 month arm and 198 patients on 36 month arm), median age was 61 years (range 22 to 84 years). The median time of follow-up was 54 months (from date of randomization to data cut-off), with a total of 83 months between the first patient randomized and the cut-off date.

The primary endpoint of the study was recurrence free survival (RFS) defined as the time from date of randomization to the date of recurrence or death from any cause.

Thirty-six (36) months of Glivec treatment significantly prolonged RFS compared to 12 months of Glivec treatment (with overall Hazard Ratio (HR)=0.46 [0.32, 0.65], p<0.0001 and a HR of 0.42 [0.28, 0.61] beyond month 12) (Table 11, Figure 4). There were 84 (42%) and 50 (25%) total RFS events for the 12-months and 36 months arms respectively.

In addition, thirty-six (36) months of Glivec treatment significantly prolonged overall survival (OS) compared to 12 months of Glivec treatment (HR=0.45 [0.22, 0.89], p=0.0187) (Table 11, Figure 5). The total number of deaths were 25 for the 12-months treatment arm and 12 for the 36-months treatment arm.

Table 11 12-month and 36-month Glivec Treatment (SSGXVIII/AIO Trial)

	12-month treatment arm	36-month treatment arm
RFS	**%(CI)**	**%(CI)**
12 mos.	93.7 (89.2-96.4)	95.9 (91.9-97.9)
24 mos.	75.4 (68.6-81.0)	90.7 (85.6-94)
36 mos.	60.1 (52.5-66.9)	86.6 (80.8-90.8)
48 mos.	52.3 (44.0-59.8)	78.3 (70.8-84.1)
60 mos.	47.9 (39.0-56.3)	65.6 (56.1-73.4)
Survival		
36 mos.	94.0 (89.5-96.7)	96.3 (92.4-98.2)
48 mos.	87.9 (81.1-92.3)	95.6 (91.2-97.8)
60 mos.	81.7 (73.0-87.8)	92.0 (85.3-95.7)

Figure 4 Kaplan-Meier estimates for primary recurrence-free survival endpoint (ITT population)

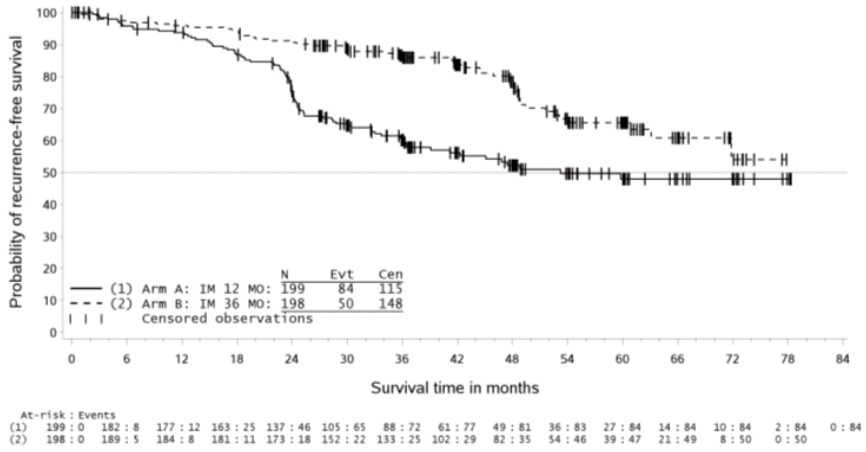
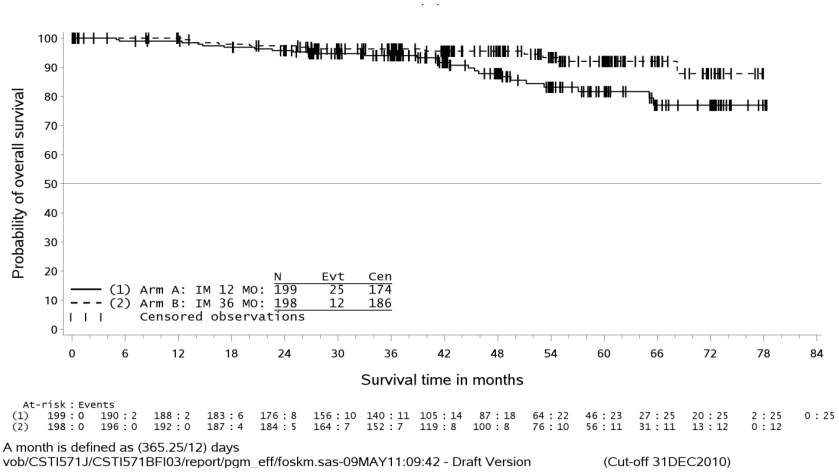


Figure 5 Kaplan-Meier estimates for overall survival (ITT population)



Clinical studies in DFSP

One open label, multicenter, phase II clinical trial (study B2225) was conducted testing Glivec in a diverse populations of patients suffering from life-threatening diseases associated with ABL, KIT or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP out of a total of 185 patients, 45 of whom had hematological diseases and 140 a variety of solid tumors. The primary evidence of efficacy for patients in the solid tumor group was based on objective response rates. The solid tumor population was treated with Glivec 800 mg daily. 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. A further 6 DFSP patients treated with Glivec are reported in 5 published case reports, their ages ranging from 18 months to 49 years. The total population treated for DFSP comprises 18 patients, 8 of them with metastatic disease. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Glivec daily. The pediatric patient received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily. Responses to treatment are described in Table 12.

Table 12 Response rate in 18 DFSP patients treated with Glivec

Tumor response	Number of patients	%
Complete response	7	39
Partial response *	8	44
Total	15	83

* 5 patients made disease free by surgery

Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of them completely (37%). The median duration of therapy in study B2225 was 6.2 months, with

a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.

Clinical studies in hepatic insufficiency

In a study of patients with varying degrees of hepatic dysfunction (mild, moderate and severe - see Table 13 below for liver function classification), the mean exposure to imatinib (dose normalized AUC) did not increase compared to patients with normal liver function. In this study, 500 mg daily was safely used in patients with mild liver dysfunction and 300 mg daily was used in other patients. Although only a 300 mg daily dose was used in patients with moderate and severe liver dysfunction, pharmacokinetic analysis projects that 400 mg can be used safely (see sections DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Table 13 Liver function classification

Liver dysfunction	Liver function 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

Clinical studies in renal insufficiency

In a study of patients with varying degrees of renal dysfunction (mild, moderate and severe - see Table 14 below for renal function classification), the mean exposure to imatinib (dose normalized AUC) increased 1.5- to 2-fold compared to patients with normal renal function, which corresponded to an elevated plasma level of AGP, a protein to which imatinib binds strongly. No correlation between imatinib exposure and the severity of renal deficiency was observed. In this study, 800 mg daily was safely used in patients with mild renal dysfunction and 600 mg daily was used in 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. Literature data showed that a daily dose of 400 mg was well tolerated in a patient with end-stage renal disease on hemodialysis. The PK plasma exposure in this patient fell within the range of values of imatinib and its metabolite CGP74588 observed in patients with normal renal function. Dialysis was not found to intervene with the plasma kinetics of imatinib. Since renal excretion represents a minor elimination pathway for imatinib, patients with severe renal insufficiency and on dialysis could receive treatment at the 400 mg starting dose. However, in

these patients caution is recommended. The dose can be reduced if not tolerated, or increased for lack of efficacy (see sections DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS FOR USE, and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Table 14 Renal function classification

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

CrCL = Creatinine Clearance

NON-CLINICAL SAFETY DATA

Imatinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and juvenile toxicity studies. Target organs associated with the pharmacological action of imatinib include bone marrow, peripheral blood, lymphoid tissues, gonads and gastrointestinal tract. Other target organs include the liver and the kidney.

No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 post-partum). In the juvenile toxicology study, transitory effects upon growth and delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average pediatric exposure at the highest recommended dose of 340 mg/m^2. Also, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average pediatric exposure at the highest recommended dose of 340 mg/m^2.

In the 2 year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) 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, representing approximately 0.5 to 4 or 0.3 to 2.4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 to 3.0 times the daily exposure in children (based on AUC) at 340 mg/m^2. 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 at 60 mg/kg/day.

The relevance of these findings in the rat carcinogenicity study for humans is not known. An analysis of the safety data from clinical trials and spontaneous adverse event reports did not

provide evidence of an increase in overall incidence of malignancies in patients treated with Glivec compared to that of the general population.

Non-neoplastic 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.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Protect from moisture.

Glivec should not be used after the date marked "EXP" on the pack.

Glivec must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements

Manufacturer:

See folding box.

International Package Leaflet

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