

AUSTRALIAN PRODUCT INFORMATION

GLIVEC (IMATINIB) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

The active ingredient is imatinib as the mesilate salt (beta crystals).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg or 400 mg of imatinib (equivalent to 119.5 mg or 478 mg imatinib mesilate, respectively).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Glivec 100 mg film-coated tablet: very dark yellow to brownish orange round tablet with imprint “NVR” on one side and “SA” and score on the other side.

Glivec 400 mg film-coated tablet: very dark yellow to brownish orange, ovaloid, biconvex tablet with “400” on one side and score on the other side and “SL” on each side of the score.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Glivec is indicated for the:

- treatment of patients with chronic myeloid leukaemia (CML)
- treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (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, where conventional therapies have failed
- treatment of adult patients with aggressive systemic mastocytosis (ASM), where conventional therapies have failed
- treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL)
- treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST)
- adjuvant treatment of adult patients at high risk of recurrence following complete gross resection of KIT (CD117)-positive primary GIST (see Dosage and Administration and Clinical Trials)
- treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The prescribed dose should be administered orally, with a meal and a large glass of water to minimise 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).

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

Monitoring of response to Glivec therapy in 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.

Dosage for CML

Adults

The recommended dosage of Glivec is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. An increase in dose from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reactions and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression at any time; failure to achieve a satisfactory haematological 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 haematological and/or cytogenetic response.

If, in patients with chronic phase disease escalated to 600 mg per day, the dose was associated with no greater than mild toxicity during the initial 4 weeks, then further dose escalation to 800 mg per day may be considered (see section 5.1 Pharmacodynamic properties – Clinical trials).

Dosage for Ph+ ALL

Adults: The recommended dose of Glivec is 600 mg/day for adult patients with Ph+ ALL.

Dosage for MDS/MPD

The recommended initial dose of Glivec is 400 mg/day for adult patients with MDS/MPD. An increase from 400 mg to 600 mg or 800 mg per day may be considered if response is inadequate.

Dosage for ASM

The recommended initial dose of Glivec is 400 mg/day for adult patients with ASM. An increase from 400 mg to 600 mg or 800 mg per day may be considered if response is inadequate.

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

Dosage for HES/CEL

The recommended initial dose of Glivec is 400 mg/day for adult patients with HES/CEL. An increase from 400 mg to 600 mg or 800 mg per day may be considered if response is inadequate.

For HES/CEL patients with demonstrated FIP1L1-PDGFR α fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100mg 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 for GIST

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

For patients who develop disease progression while receiving 400mg/day, a dose increase to 800mg/day may be considered. There are limited data on the efficacy of increasing dose from 600 to 800mg/day. Treatment with Glivec in GIST patients should be continued until disease progression.

The recommended dose of Glivec is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. In clinical trials one year of Glivec and three years of Glivec were studied. In the patient population defined in Study SSG XVIII/AIO, three years of Glivec is recommended (see section 5.1 Pharmacodynamic properties - Clinical Trials). The optimal treatment duration with Glivec is not known.

Dosage for DFSP

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

Dose Adjustments for Adverse Drug Reactions

Non-haematological adverse drug reactions

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

If elevations in bilirubin $> 3 \times$ institutional upper limit of normal (IULN) or in liver transaminases $> 5 \times$ IULN occur, Glivec should be withheld until bilirubin levels have returned to $<1.5 \times$ IULN and transaminase levels to $<2.5 \times$ IULN. Treatment with Glivec may then be continued at a reduced daily dose. In adults the daily dose should be reduced from 400 mg to 300 mg or from 600 mg to 400 mg, or from 800 mg to 600 mg. In children the daily dose should be reduced from 340 mg/m² to 260 mg/m².

In adjuvant GIST, if non haematological toxicity of grade 2 is experienced, imatinib should be withheld until the toxicity has resolved to \leq grade 1. Treatment can be resumed at the previous dose, however, if grade 2 toxicity recurs, treatment should be withheld and then re-introduced at a

reduced dose of 300 mg per day. If grade 3/4 toxicity occurs, treatment is withheld until toxicity resolves to \leq grade 1. The daily dose is resumed at a reduced dose of 300 mg per day.

Haematological adverse drug reactions

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

Dose adjustments for neutropenia and thrombocytopenia

SM associated with eosinophilia or HES/CEL with FIP1L1-PDGFR α fusion kinase (starting dose 100 mg)	ANC < $1.0 \times 10^9/L$ and/or platelets < $50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Glivec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Glivec at the original starting dose (i.e. before severe adverse drug reaction)
Chronic phase CML (starting dose 400 mg in adults) MDS/MPD, SM and HES/CML (starting dose 400 mg) GIST (starting dose either 400 mg or 600 mg)	ANC < $1.0 \times 10^9/L$ and/or platelets < $50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Glivec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Glivec at the original starting dose (i.e. before severe adverse drug reaction) 3. In the event of recurrence of ANC < $1.0 \times 10^9/L$ and/or platelets < $50 \times 10^9/L$, repeat step 1 and resume Glivec at a reduced dose for CML, MDS/MPD, SM or HES/CEL of 300 mg in adults or 200 mg/m² in children or for GIST of 300 mg if starting dose was 400 mg or 400 mg if starting dose was 600 mg.
Adjuvant GIST	ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Glivec until toxicity resolved to \leq grade 2. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse drug reaction) 3. In the event of recurrence or persistence for longer than 2 weeks, repeat step 1 at reduced dose of 300 mg once daily. 4. If treatment was interrupted for 4 weeks or longer, then treatment should be discontinued.
Paediatric chronic phase CML (at dose 340 mg/m ²)	ANC < $1.0 \times 10^9/L$ and/or platelets < $50 \times 10^9/L$	<ol style="list-style-type: none"> 1. Stop Glivec until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse drug reaction) 3. In the event of recurrence of ANC < $1.0 \times 10^9/L$ and/or platelets < $50 \times 10^9/L$, repeat step 1 and resume Glivec at reduced dose of 260 mg/m².
Accelerated phase CML, blast crisis and Ph+ ALL (starting dose 600 mg in adults or 340 mg/m ² in children)	¹ ANC < $0.5 \times 10^9/L$ and/or platelets < $10 \times 10^9/L$	<ol style="list-style-type: none"> 1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of Glivec to 400 mg in adults or 260 mg/m² in children. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg in adults or 200 mg/m² in children. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Glivec until ANC $\geq 1 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$, then resume treatment at 300 mg in adults or 200 mg/m² in children.

DFSP (starting dose 800 mg)	ANC < 1.0 x10 ⁹ /L and/or platelets < 50 x10 ⁹ /L	<ol style="list-style-type: none"> 1. Stop Glivec until ANC ≥ 1.5 x10⁹/L and platelets ≥ 75 x10⁹/L. 2. Resume treatment with Glivec at 600 mg 3. In the event of recurrence of ANC < 1.0 x10⁹/L and/or platelets < 50 x10⁹/L, repeat step 1 and resume Glivec at reduced dose of 400 mg.
ANC = absolute neutrophil count ¹ occurring after at least 1 month of treatment		

Special populations

Children

Dosing for children should be on the basis of body surface area (mg/m²). The dose 340 mg/m² daily is recommended for children with chronic phase CML 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.

The dosing recommendation is currently based on a small number of paediatric patients (see section 5.2 Pharmacokinetic properties and section 5.1 Pharmacodynamic properties – Clinical trials). There is no experience with the use of Glivec in children 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 children in other indications.

Recommendations for dose reduction in children are extrapolations based on practice in adults, as data in children are extremely limited (refer to dosage table above).

Hepatic insufficiency

Imatinib is metabolised by the liver. Patients with mild or moderate liver dysfunction should be given the minimum recommended dose of 400 mg daily, and patients with severe liver dysfunction should start at 300 mg daily (see section 5.2 Pharmacokinetic properties). The dose can be reduced if the patient develops unacceptable toxicity (see section 4.2 Dose and method of administration - Dose Adjustments for Adverse Drug Reactions).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction could be given the minimum recommended dose of 400 mg daily as starting dose (see section 5 Pharmacological properties). 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 4.4 Special warnings and precautions for use).

Elderly patients

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. Decrease in hemoglobin and increased blood creatinine showed a different incidence with age in the adjuvant 36-month trial in GIST. No specific dose recommendation is necessary in the elderly.

Patient Monitoring

Complete blood counts must be performed regularly during therapy with Glivec and liver function (transaminases, bilirubin, alkaline phosphatase) should also be monitored regularly (see section 4.4 Special warnings and precautions for use - Haematological toxicity and Use in hepatic impairment). Patients should be weighed regularly (see section 4.4 Special warnings and precautions for use - Fluid retention and oedema). Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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. ciclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives) (see section 4.5 Interactions with other medicines and other forms of interactions).

Fluid retention and oedema

Glivec is often associated with oedema and occasionally serious fluid retention (see section 4.8 Adverse effects (Undesirable effects)). Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of oedema was increased with higher imatinib dose in the CML studies. Severe fluid retention (pleural effusion, pericardial effusion, pulmonary oedema, ascites) was reported in 2 to 8% of patients taking Glivec for CML. In addition, severe superficial oedema was reported in 2-5% of the patients with CML. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Severe superficial oedema and severe fluid retention (pleural effusion, pulmonary oedema and ascites) were reported in 89 patients (11%) taking 400 mg and in 127 (16%) taking 800 mg in the combined Phase III trials of patients taking Glivec for GIST.

Haematological toxicity

Complete blood counts must be performed regularly during therapy with Glivec. Treatment of CML patients with Glivec has been associated with neutropenia or thrombocytopenia and anaemia. 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 may be reduced (see section 4.2 Dose and method of administration - Haematological adverse drug reactions).

Gastrointestinal Haemorrhage

In the Phase III studies in patients with unresectable or metastatic malignant GIST 211 patients (12.9%) reported Grade 3/4 haemorrhage at any site. In the Phase II study in patients with unresectable or metastatic malignant GIST (study B2222), eight patients (5.4%) were reported to have had gastrointestinal (GI) haemorrhage and four patients (2.7%) were reported to have had haemorrhages at the site of tumour deposits. Of these, seven patients (5%) suffered events of grade III/IV severity.

The tumour haemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumour lesions. GI sites of tumour may have contributed to reports of GI bleeding in this 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. Onset of bleeding did not correlate with platelet count, tumour burden or duration of treatment. Fatal haemorrhages have been reported in other studies of imatinib in GIST.

Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with Glivec. When needed, Glivec discontinuation may be considered.

Tumour lysis syndrome

Cases of tumour 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 4.8 Adverse effects (Undesirable effects)).

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for Glivec (see section 4.8 Adverse effects (undesirable effects)). If laboratory or clinical findings associated with TMA occur in a patient receiving Glivec, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Glivec should not be resumed.

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 of hepatitis B reactivation 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 4.8 Adverse effects (Undesirable effects)).

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.

Use in hepatic impairment

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib (see section 4.8 Adverse effects (Undesirable effects)). Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Glivec. Laboratory abnormalities should be managed with interruption of treatment and/or dose reduction (see section 4.2 Dose and method of administration - Non-haematological adverse drug reactions).

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see section 4.8 Adverse effects (Undesirable effects)). It is not known whether Glivec can exacerbate existing liver dysfunction.

When Glivec is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where Glivec is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.8 Adverse effects (Undesirable effects)).

One patient, who was taking paracetamol regularly for fever, died of acute liver failure. Although the aetiology is currently unknown, special caution should be exercised when using paracetamol. Patients should be warned to avoid or restrict the use of over-the-counter and prescription medicines containing paracetamol.

Severe congestive heart failure and left ventricular dysfunction

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported in patients taking Glivec. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomised phase III study in 1106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Glivec compared to 0.9% of patients taking IFN + Ara-C.

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 failure or renal failure should be evaluated and treated.

Hypereosinophilic cardiac toxicity

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 imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Myelodysplastic (MDS)/myeloproliferative (MPD) diseases and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with Glivec should be considered at the initiation of therapy.

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Glivec. Thyroid stimulating hormone (TSH) levels should be closely monitored in such patients.

Use in renal impairment

Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib 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.

Glivec 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 section 4.2 Dose and method of administration and section 5 Pharmacological properties).

Use in the elderly

See section 4.2 Dose and Method of Administration – Special Populations – Elderly Patients.

Paediatric use

Glivec efficacy and safety have been demonstrated in children with Ph+ chronic phase CML and in Ph+ALL. There is no experience with Glivec in children with accelerated phase CML below 2 years of age and with Ph+ALL below 1 year of age, and very limited experience in children with blast crisis.. There is very limited experience with Glivec in children under 3 years of age (see section 5.1 Pharmacodynamic properties – Clinical trials - Paediatric patients).

There have been case reports of growth retardation occurring in children and pre-adolescents receiving Glivec. The long term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended.

Effects on laboratory tests

Interference of GLIVEC with laboratory and/or diagnostic tests has not been studied.

Toxicities from long-term use

Because follow-up of most patients treated with imatinib is relatively short (<6 months), it is important to consider potential toxicities suggested by animal studies, specifically, liver and kidney toxicity and immunosuppression. (See section 5.3 Preclinical safety data)

Phototoxicity

Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be advised to protect skin from sunlight with

protective clothing and high sun protection factor (SPF) sunscreen; and avoid sunlamps and tanning beds.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that may alter imatinib plasma concentrations

Drugs that may increase imatinib plasma concentrations

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity 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 (e.g. ketoconazole, erythromycin, clarithromycin, itraconazole, HIV antivirals, grapefruit juice).

Drugs that may decrease imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital (phenobarbitone), or St. John's wort [*Hypericum perforatum*]) 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 the oral-dose clearance of imatinib by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold). This represents mean decreases in 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, oxcarbamazepine, phenytoin, fosphenytoin, phenobarbital (phenobarbitone) and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. In two published studies, concomitant administration of imatinib and a product containing St. John's wort led to a 30-32% reduction in the AUC of Glivec.

Co-administration of rifampicin or other CYP3A4 inducers should be avoided wherever possible. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs that may have their plasma concentration altered by Glivec

Imatinib 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. ciclosporin, pimozide). Glivec will increase plasma concentrations of other CYP3A4 metabolised drugs (e.g. triazole-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc).

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.

Commonly used drugs metabolised by CYP2D6 include some antidepressants, neuroleptics and anti-arrhythmic agents.

In-vitro data suggest that imatinib has some capacity to act as an inhibitor of CYP2C9 and CYP2C19, although at concentrations higher than would be expected in plasma with recommended doses. However, caution should be exercised with the concomitant use of drugs metabolised by CYP2C9, especially those with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives). PT prolongation was observed following co-administration with warfarin. In view of the potential interaction between Glivec and warfarin, the international normalised ratio (INR) of patients who require anticoagulation with warfarin should be monitored closely, especially when Glivec dose adjustments are necessary. Consideration should be given to anticoagulation with low-molecular weight heparin or unfractionated heparin.

Glivec inhibits paracetamol O-glucuronidation *in vitro* with K_i value of 58.5 micromol/L. The inhibition was not observed *in vivo* in Korean CML patients after co-administration of Glivec (400 mg/day between days two and eight) and paracetamol (1000 mg/day on day eight). Glivec pharmacokinetics were not altered by paracetamol. Exercise caution in non-Korean patients when co-administering Glivec and paracetamol. Also exercise caution with concomitant use of Glivec at doses > 400 mg/day or the chronic use of concomitant paracetamol and Glivec (see section 4.4 Special warnings and precautions for use).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a study of fertility, in which male rats were dosed orally for 70 days prior to mating and female rats were dosed for 14 days prior to mating and through to gestational day 6, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg (approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area). This was not seen at doses \leq 20 mg/kg (one-fourth the maximum human dose of 800 mg). There was no effect on mating or on number of pregnant females. At 60 mg/kg, but not at doses \leq 20 mg/kg, female rats had significant post-implantation fetal loss and a reduced number of live fetuses.

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.

Use in pregnancy – Pregnancy Category D

Women of childbearing potential must be advised to use highly effective contraception during treatment (methods that result in less than 1% pregnancy rate) and for at least 15 days after stopping treatment with Glivec.

There are no clinical trials on the use of Glivec in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Glivec.

Glivec should be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus. If Glivec is used during pregnancy, or if the patient becomes pregnant while taking Glivec,

the patient should be apprised of the potential risk to the foetus. Imatinib mesilate was teratogenic in rats when administered during organogenesis at oral doses ≥ 30 mg/kg, approximately equal to one third the maximum clinical dose of 800 mg/day, based on body surface area. Teratogenic effects included exencephaly or encephalocele, protruded tongue, absent/reduced frontal and absent parietal bones. Female rats also experienced significant post-implantation loss in the form of early fetal resorptions at doses >30 mg/kg, with total fetal loss in all animals at doses >100 mg/kg.

Administration of imatinib to rats from early gestation through weaning at an oral dose of 45 mg/kg/day (approximately half the maximal clinical dose of 800 mg/day based on body surface area) resulted in an increase in postimplantation loss. Additionally, F₁ offspring showed reproductive effects (including decreased numbers of implantation sites, increased numbers of resorptions and decreased numbers of viable foetuses). Mild maternotoxicity was also observed at this dose.

Use in lactation

Both imatinib and its active metabolite can be distributed into human milk. 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 low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking Glivec should not breast feed. Administration of imatinib to rats from early gestation through weaning at an oral dose of 45 mg/kg/day (approximately half the maximal clinical dose of 800 mg/day based on body surface area) resulted in delayed preputial separation and a decrease in pup viability (day 0-4 postpartum).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Reports of motor vehicle accidents have been reported 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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, diarrhea, 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 event.

The safety profile of Glivec in adult and paediatric patients with Ph+ Leukaemias is similar in regards to the types of events experienced.

In the GIST study B2222, the percentage of some adverse reactions was higher in the patients with newly-diagnosed CML in whom the dose was increased to 800 mg daily compared to the population

of patients before dose increase. These more frequent adverse reactions included gastrointestinal haemorrhages, conjunctivitis and elevation of transaminases or bilirubin.

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-tumoral haemorrhages in GIST patients and are probably due to disease-related factors. The most frequent event by system organ class in CML and GIST treatment were GI disorders, skin and subcutaneous tissue disorders, general disorders and administration site conditions, and musculoskeletal and connective tissue disorders.

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.

Adverse reactions

Adverse reactions with suspected relationship, reported as more than an isolated case, are listed below by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$) including isolated reports. Adverse reactions and their frequencies reported in the table below are based on the registration studies for CML and GIST.

Adverse reactions in clinical studies for CML and GIST

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

Body as a whole

Very common:	fluid retention and oedema, fatigue, weight increased
Common:	pyrexia, weakness, rigors, anasarca, chills, weight decreased
Uncommon:	chest pain, malaise, blood creatine phosphokinase increased, blood lactate dehydrogenase increased
Rare:	blood amylase increased

Cardiac disorders

Uncommon:	cardiac failure congestive ¹ , pulmonary oedema, palpitations, tachycardia
Rare:	pericardial effusion, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris

Ear and labyrinth disorders

Uncommon: vertigo, tinnitus, hearing loss

Eye disorders:

Common: eyelid oedema, conjunctivitis, lacrimation increased, conjunctival haemorrhage, dry eye, vision blurred

Uncommon: eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema

Rare: cataract, papilloedema, glaucoma

Gastrointestinal disorders

Very common: nausea, vomiting, diarrhoea, dyspepsia, abdominal pain²

Common: abdominal distension, flatulence, constipation, gastro-oesophageal reflux, dry mouth, gastritis

Uncommon: stomatitis, mouth ulceration, gastrointestinal haemorrhage³, melaena, ascites, gastric ulcer, oesophagitis, haematemesis, cheilitis, dysphagia, pancreatitis

Rare: colitis, ileus, inflammatory bowel disease

Hepato-biliary disorders

Very Common: increased hepatic enzymes

Common: hyperbilirubinaemia

Uncommon: jaundice, hepatitis, blood alkaline phosphatase increased,

Rare: hepatic failure⁴, hepatic necrosis⁴

Infections and infestations

Very Common: Upper respiratory tract infection

Uncommon: sepsis, nasopharyngitis, pneumonia⁵, sinusitis, cellulitis, herpes simplex, herpes zoster, influenza, urinary tract infection, gastroenteritis

Rare: fungal infection

Metabolism and nutrition disorders

Common: anorexia

Uncommon: dehydration, hyperuricaemia, hypokalaemia, appetite increased, appetite decreased, gout, hypophosphataemia, hypercalcaemia, hyperglycaemia, hyponatraemia

Rare: hyperkalaemia, hypomagnesaemia

Musculoskeletal, connective tissue and bone disorders

Very common: muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain⁶

Common: joint swelling

Uncommon: joint and muscle stiffness

Rare: muscular weakness, arthritis

Nervous system disorders

Very common: headache⁷

Common: dizziness, taste disturbance, paraesthesia, hypoaesthesia

Uncommon: cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor

Rare: optic neuritis, increased intracranial pressure, convulsions

Psychiatric disorders

Common: insomnia
Uncommon: depression, anxiety, libido decreased
Rare: confusion

Renal and urinary disorders

Very Common: Blood creatinine increased⁸
Uncommon: renal failure, renal pain, urinary frequency increased, haematuria

Reproductive system and breast disorders

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

Respiratory, thoracic and mediastinal disorders

Common: epistaxis, dyspnoea, cough
Uncommon: pleural effusion⁹, pharyngolaryngeal pain, pharyngitis
Rare: pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage

Skin and subcutaneous tissue disorders

Very common: periorbital oedema, dermatitis/eczema/rash
Common: face oedema, pruritus, erythema, dry skin, alopecia, night sweats, photosensitivity reaction
Uncommon: petechiae, sweating increased, urticaria, ecchymosis, increased tendency to bruise, onychoclasia, folliculitis, purpura, contusion, hypotrichosis, rash pustular, skin hypopigmentation, skin hyperpigmentation, psoriasis, exfoliative dermatitis, bullous eruptions
Rare: erythema multiforme, leucocytoclastic vasculitis, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, acute generalised exanthematous pustulosis (AGEP)

Vascular disorders

Common: Flushing¹⁰, haemorrhage
Uncommon: haematoma, subdural haematoma, hypertension, hypotension, peripheral coldness, Raynaud's phenomenon
Rare: thrombosis/embolism

- ¹ 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
- ^{2,3} Abdominal pain and gastrointestinal haemorrhage were most commonly observed in patients with CML than in GIST patients
- ⁴ Some fatal cases of hepatic failure and hepatic necrosis have been reported
- ⁵ Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST
- ⁶ Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients
- ⁷ Headache was most common in GIST patients
- ⁸ Most of the blood creatinine increases were of mild severity (grade 1)
- ⁹ 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
- ¹⁰ Flushing was most common in GIST patients and bleeding (haematoma, haemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC)

Adverse events in CML clinical trials in adults

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated in the Phase III study of Glivec versus IFN+Ara-C (Study 0106) and in the single-arm CML studies 0102, 0109 and 0110 are shown in Tables 1 and 2, respectively.

Table 1. Adverse events reported in CML patients in Study 0106 (≥10% of all patients in either arm) ⁽¹⁾

	All Grades		CTC Grades 3/4	
	Glivec N=551 (%)	IFN+Ara-C N=533 (%)	Glivec N=551 (%)	IFN+Ara-C N=533 (%)
Preferred Term				
Fluid Retention	59.2	10.7	1.8	0.9
- Superficial oedema	57.5	9.2	1.1	0.4
- Other Fluid Retention Events ²	6.9	1.9	0.7	0.6
Nausea	47.0	61.5	0.9	5.1
Muscle Cramps	43.2	11.4	1.6	0.2
Musculoskeletal Pain	39.2	44.1	3.4	8.1
Diarrhoea	38.5	42.0	2.0	3.2
Rash and Related Terms	37.2	25.7	2.4	2.4
Fatigue	37.0	66.8	1.6	25.0
Headache	33.6	43.3	0.5	3.6
Joint Pain	30.3	39.4	2.5	7.3
Abdominal Pain	29.9	25.0	2.5	3.9
Nasopharyngitis	26.9	8.4	0	0.2
Haemorrhage	24.1	20.8	1.1	1.5
- GI Haemorrhage	1.3	1.1	0.5	0.2
- CNS Haemorrhage	0.2	0.2	0	0.2
Myalgia	22.5	38.8	1.5	8.1
Vomiting	20.5	27.4	1.5	3.4
Dyspepsia	17.8	9.2	0	0.8
Cough	17.4	23.1	0.2	0.6
Pharyngolaryngeal Pain	16.9	11.3	0.25	0
Upper Respiratory Tract Infection	16.5	8.4	0.2	0.4
Dizziness	15.8	24.2	0.9	3.6
Pyrexia	15.4	42.4	0.9	3.0
Weight Increased	15.2	2.1	1.6	0.4
Insomnia	13.2	18.8	0	2.3
Depression	12.7	35.8	0.5	13.1
Influenza	11.1	6.0	0.2	0.2

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

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

Table 2. Adverse events reported in CML patients in Studies 0102, 0109 and 0110 (≥10% of all patients in any trial)⁽¹⁾

Preferred Term	Myeloid Blast Crisis (N= 260) %		Accelerated Phase (N=235) %		Chronic Phase, IFN Failure (N=532) %	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid Retention	72	11	76	6	69	4
- Superficial oedema	66	6	74	3	67	2
- Other Fluid Retention Events ⁽²⁾	22	6	15	4	7	2
Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2
Diarrhoea	43	4	57	5	48	3
Haemorrhage	53	19	49	11	30	2
- CNS Haemorrhage	9	7	3	3	2	1
- GI Haemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnoea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2

Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalaemia	13	4	9	2	6	0.8
Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	0.4	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

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

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

Adverse events in paediatric CML clinical trials

Experience is limited in patients aged ≤ 18 years treated with imatinib in clinical trials. In these trials, the toxicity of imatinib appeared comparable to that seen in adults. Toxicities included grade 3 or 4 cytopenias involving neutropenia and thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

Adverse events in the unresectable and/or malignant metastatic GIST clinical trial

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of patients treated in the GIST study are shown in Table 3.

Table 3. Adverse experiences reported in GIST clinical trial ($\geq 10\%$ of all patients)⁽¹⁾

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

Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1
Headache	33	39	0	0
Flatulence	30	34	0	0
Any Haemorrhage	26	34	6	11
- Tumour Haemorrhage	1	4	1	4
- Cerebral Haemorrhage	1	0	1	0
- GI Tract Haemorrhage	4	4	4	3
- Other Haemorrhage	22	27	0	5
Pyrexia	25	16	3	0
Back Pain	23	26	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper Respiratory Tract Infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0
Loose Stools	12	10	0	0
Operation	12	8	6	4
Pharyngolaryngeal Pain	12	7	0	0
Joint Pain	11	15	1	0
Constipation	11	10	0	1
Anxiety	11	7	0	0
Taste Disturbance	3	15	0	0
⁽¹⁾ All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.				

Adverse events in the adjuvant treatment of GIST clinical trials

In study Z9001, the majority of both Glivec and placebo treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include diarrhoea, fatigue, nausea, oedema, decreased haemoglobin, rash, vomiting and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST. Drug was discontinued for adverse reactions in 57 patients (17%) and 11 patients (3%) of the Glivec and placebo treated patients respectively. Oedema, gastrointestinal disturbances (nausea, vomiting, abdominal distension and diarrhoea), fatigue, low haemoglobin and rash were the most frequently reported adverse reactions at the time of discontinuation.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Glivec are shown in Table 4.

Table 4. Adverse experiences reported in the Adjuvant GIST clinical trial Z9001 (≥10% of all patients)⁽¹⁾

	All CTC Grades		CTC Grade 3 and above	
	Glivec (N=337)	Placebo (N=345)	Glivec (N=337)	Placebo (N=345)
Preferred Term	%	%	%	%
Diarrhoea	59.3	29.3	3.0	1.4
Fatigue	57.0	40.9	2.1	1.2
Nausea	53.1	27.8	2.4	1.2
Periorbital Oedema	47.2	14.5	1.2	0
Haemoglobin Decreased	46.9	27.0	0.6	0
Peripheral Oedema	26.7	14.8	0.3	0
Rash (Exfoliative)	26.1	12.8	2.7	0
Vomiting	25.5	13.9	2.4	0.6
Abdominal Pain	21.1	22.3	3.0	1.4
Headache	19.3	20.3	0.6	0
Dyspepsia	17.2	13.0	0.9	0
Anorexia	16.9	8.7	0.3	0
Weight Increased	16.9	11.6	0.3	0
Liver enzymes (ALT) Increased	16.6	13.0	2.7	0
Muscle spasms	16.3	3.3	0	0
Neutrophil Count Decreased	16.0	6.1	3.3	0.9
Arthralgia	15.1	14.5	0	0.3
White blood cell count decreased	14.5	4.3	0.6	0.3
Constipation	12.8	17.7	0	0.3
Dizziness	12.5	10.7	0	0.3
Liver Enzymes (AST) Increased	12.2	7.5	2.1	0
Myalgia	12.2	11.6	0	0.3
Blood Creatinine Increased	11.6	5.8	0	0.3
Cough	11.0	11.3	0	0
Pruritus	11.0	7.8	0.9	0
Weight Decreased	10.1	5.2	0	0
¹ All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment. A patient with multiple occurrences of an adverse event is counted only once in the adverse event category.				

The adjuvant trial SSG XVIII/AIO compared 1 year and 3 years Glivec treatment. Table 5 shows adverse events, regardless of relationship to study drug, that were reported in at least 5% of patients treated with Glivec.

There was a higher incidence of severe (Grade 3-4) and serious adverse events in the 3-year group than the 1-year group but this was expected because of the longer duration of treatment. Discontinuations due to adverse events were also greater in the 3-year group (13.6%) than the 1-year group (7.7%).

Adverse events were generally consistent with the known safety profile of Glivec. There was insufficient data to assess long-term safety.

Table 5. Adverse Events Regardless of Relationship to Study Drug by Preferred Term All Grades and 3/4 Grades (≥5% of Glivec Treated Patients) SSG XVIII/AIO Trial⁽¹⁾

Preferred Term	All CTC Grades		CTC Grades 3 and above	
	Glivec 12 Months (N=194) %	Glivec 36 Months (N=198) %	Glivec 12 Months (N=194) %	Glivec 36 Months (N=198) %
Patients with at least one AE	99.0	100.0	20.1	32.8
Haemoglobin decreased	72.2	80.3	0.5	0.5
Periorbital oedema	59.3	74.2	0.5	1.0
Blood lactate dehydrogenase increased	43.3	60.1	0	0
Diarrhoea	43.8	54.0	0.5	2.0
Nausea	44.8	51.0	1.5	0.5
Muscle spasms	30.9	49.0	0.5	1.0
Fatigue	48.5	48.5	1.0	0.5
White blood cell count decreased	34.5	47.0	2.1	3.0
Pain	25.8	45.5	1.0	3.0
Blood creatinine increased	30.4	44.4	0	0
Oedema peripheral	33.0	40.9	0.5	1.0
Dermatitis	29.4	38.9	2.1	1.5
Aspartate aminotransferase increased	30.9	37.9	1.5	3.0
Alanine aminotransferase increased	28.9	34.3	2.1	3.0
Neutrophil count decreased	24.2	33.3	4.6	5.1
Hypoproteinaemia	23.7	31.8	0	0
Infection	13.9	27.8	1.5	2.5
Weight increased	13.4	26.8	0	0.5
Pruritus	12.9	25.8	0	0
Flatulence	19.1	24.7	1.0	0.5
Vomiting	10.8	22.2	0.5	1.0
Dyspepsia	17.5	21.7	0.5	1.0
Hypoalbuminaemia	11.9	21.2	0	0
Oedema	10.8	19.7	0	0.5
Abdominal distension	11.9	19.2	0.5	0
Headache	8.2	18.2	0	0
Lacrimation increased	18.0	17.7	0	0
Arthralgia	8.8	17.2	0	1.0
Blood alkaline phosphatase increased	10.8	16.7	0	0.5
Dyspnoea	6.2	16.2	0.5	1.5
Myalgia	9.3	15.2	0	1.0
Platelet count decreased	11.3	14.1	0	0
Blood bilirubin increased	11.3	13.1	0	0
Dysgeusia	9.3	12.6	0	0
Paraesthesia	5.2	12.1	0	0.5
Vision blurred	10.8	11.1	1.0	0.5
Alopecia	11.3	10.6	0	0
Decreased appetite	9.8	10.1	0	0
Constipation	8.8	9.6	0	0
Pyrexia	6.2	9.6	0	0
Depression	3.1	8.1	0	0
Abdominal pain	2.6	7.6	0	0
Conjunctivitis	5.2	7.6	0	0
Photosensitivity reaction	3.6	7.1	0	0
Dizziness	4.6	6.6	0.5	0
Haemorrhage	3.1	6.6	0	0
Dry skin	6.7	6.1	0.5	0
Nasopharyngitis	1.0	6.1	0	0.5
Palpitations	5.2	5.1	0	0

⁽¹⁾All adverse events occurring in $\geq 5\%$ of patients are listed regardless of suspected relationship to treatment. A patient with multiple occurrences of an adverse event is counted only once in the adverse event category.

Adverse events with imatinib observed in trials in Ph+ ALL, MDS/MPD, SM, HES/CEL and DFSP were generally consistent with those seen in CML and GIST studies.

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, the 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 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 reduction of the dose or an interruption of treatment with Glivec, but rarely require discontinuation. 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 5% and 0%, respectively of GIST patients.

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 leukemic 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. Most patients with oedema and fluid retention were elderly (>65 years old).

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. 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 that can fade despite continued therapy, has been reported. 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 drug rash with eosinophilia and systemic symptoms (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.

Hypophosphatemia

Low serum phosphate and hypophosphatemia (up to Grade 3/4) 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 hypophosphatemia 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 3/4 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, tumour necrosis may occur in the context of tumour response, rarely leading to perforation. GI obstruction/ileus occurred most commonly in the GIST population where it may be caused by tumour 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 4.4 Special warnings and precautions for use).

Growth retardation in children

Glivec appears to affect the stature of children, especially children who are pre-pubertal. A causal relationship between growth retardation in children and Glivec treatment could not be ruled out although for some cases of growth retardation there was limited information. (see section 4.4 Special warnings and precautions for use).

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

In adult patients with CML, 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 (refer Table 2 and 3). 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 $<1.0 \times 10^9/L$) and thrombocytopenias (platelet count $<50 \times 10^9/L$) being between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase CML (refer Table 6 and 7). In the randomised Phase III study in newly diagnosed CML patients, the median time to onset of neutropenia and thrombocytopenia was 44 days (range 7-463) and 43 days (range 8-421), 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 reduction of the dose or an interruption of treatment with Glivec, but can in rare cases lead to permanent discontinuation of treatment.

In paediatric 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 neutropenias 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 (see Table 8). The decreases in WBC and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

In patients with CML, grade 3 or 4 elevations of serum transaminases was common and grade 3 or 4 elevation of serum bilirubin was uncommon (see Tables 6-7), except for patients with CML in accelerated phase or blast crisis, where grade 3 elevations were common. The median duration of these episodes was approximately one week. Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of CML patients.

In patients with advanced or metastatic GIST, grade 3 or 4 elevations of serum transaminases or bilirubin were common (Table 8). In patients with GIST treated in the adjuvant setting, Grade 3 or 4 elevations of serum transaminases was common and grade 3 or 4 elevations of serum bilirubin was absent (Table 9).

Grade 3 or 4 elevations of serum transaminases or bilirubin are usually managed with dose reduction or interruption. There have been cases of cytolytic and cholestatic hepatitis and hepatic failure, some of which have been fatal (see section 4.4 Special warnings and precautions for use – Use in hepatic impairment).

Table 6. Laboratory Abnormalities in Clinical Trials with newly diagnosed CML

	Glivec® N=551 %		IFN+Ara-C N=533 %	
CTC Grades	3	4	3	4
Haematology Parameters				
- Neutropenia*	12.3	3.1	20.8	4.3
- Thrombocytopenia*	8.3	0.2	15.9	0.6
- Anaemia	3.1	0.9	4.1	0.2
Biochemistry Parameters				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.7	0.2	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated AST	2.9	0.2	3.8	0.4
- Elevated ALT	3.1	0.4	5.6	0

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

Table 7. Lab Abnormalities in Other CML Clinical Trials

	Myeloid Blast Crisis (N=260) 600 mg N=223 400 mg N=37 %		Accelerated Phase (N=235) 600 mg N=158 400 mg N=77 %		Chronic Phase, IFN Failure (N=532) 400 mg %	
CTC Grades	3	4	3	4	3	4
Haematology Parameters						
- Neutropenia	16	48	23	36	27	9
- Thrombocytopenia	30	33	31	13	21	<1
- Anaemia	42	11	34	7	6	1
Biochemistry Parameters						
- Elevated Creatinine	1.5	0	1.3	0	0.2	0
- Elevated Bilirubin	3.8	0	2.1	0	0.6	0
- Elevated Alkaline Phosphatase	4.6	0	5.5	0.4	0.2	0
- Elevated AST	1.9	0	3.0	0	2.3	0
- Elevated ALT	2.3	0.4	4.3	0	2.1	0

CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade 3 $\geq 10-50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anaemia (haemoglobin $\geq 65-80$ g/L, Grade 4 < 65 g/L), elevated creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN), elevated AST or ALT (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN)

Table 8. Laboratory Abnormalities in advanced/metastatic GIST Trial

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

CTC Grades: neutropenia (Grade 3 $\geq 0.5-1.0 \times 10^9/L$, Grade 4 $< 0.5 \times 10^9/L$), thrombocytopenia (Grade 3 $\geq 10-50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$), anemia (Grade 3 $\geq 65-80$ g/L, grade 4 < 65 g/L), elevated creatinine (Grade 3 $> 3-6$ x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin (Grade 3 $> 3-10$ x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase, ALT or AST (Grade 3 $> 5-20$ x ULN, Grade 4 > 20 x ULN), albumin (Grade 3 < 20 g/L)

Table 9. Laboratory Abnormalities in 3-year Adjuvant GIST Trial

	Arm 1: 12 months (N=194) %	Arm 2: 36 months (N=198) %
CTC Grades	3-4	3-4
Hematology Parameters		
- Hemoglobin	0.5	0.5
- Platelet count decreased	0	0
- Neutrophils count decreased	4.6	5.1
Biochemistry Parameters		
- Blood Creatinine increased	0	0
- Hypoalbuminaemia	0	0
- Elevated Bilirubin	0	0
- Elevated Alkaline Phosphatase	0	0.5
- Elevated AST	1.5	3
- Elevated ALT	2.1	3

CTC Grades: neutropenia (Grade 3 ≥ 0.5 -1.0 x 10⁹/L, Grade 4 < 0.5 x 10⁹/L), thrombocytopenia (Grade 3 ≥ 10 - 50 x 10⁹/L, Grade 4 < 10 x 10⁹/L), anemia (Grade 3 ≥ 65 -80 g/L, grade 4 < 65 g/L), elevated creatinine (Grade 3 > 3 -6 x upper limit normal range [ULN], Grade 4 > 6 x ULN), elevated bilirubin (Grade 3 > 3 -10 x ULN, Grade 4 > 10 x ULN), elevated alkaline phosphatase, ALT or AST (Grade 3 > 5 -20 x ULN, Grade 4 > 20 x ULN), albumin (Grade 3 < 20 g/L)

Laboratory abnormalities with imatinib observed in trials in Ph+ ALL, MDS/MPD, SM, HES/CEL and DFSP were generally consistent with those seen in CML and GIST studies.

The following lists the types of ADRs that 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 programmes. 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.

Adverse 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 erythrodysesthesia 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

Unknown: 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

Renal and urinary disorders

Unknown: Chronic renal failure

Blood and Lymphatic disorders

Rare: Thrombotic microangiopathy

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at

www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

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

Adult overdose: 1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, 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.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

ATC code

Pharmacotherapeutic group: BCR-ABL-tyrosine kinase inhibitor, ATC code: L01EA01.

5.1 PHARMACODYNAMIC PROPERTIES

Imatinib mesilate is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (CML). It inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines, as well as fresh leukaemic cells from CML patients. In colony formation assays using peripheral blood and bone marrow samples from CML patients, imatinib shows inhibition of formation of BCR-ABL positive colonies.

In vitro studies demonstrate imatinib is not entirely selective; it also inhibits 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 tumour (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 myelodysplastic/myeloproliferative diseases (MDS/MPD), hypereosinophilic syndrome and/or

chronic eosinophilic leukaemia (HES/CEL) and dermatofibrosarcoma protuberans (DFSP). In addition constitutive activation of KIT or PDGFR has been implicated in the pathogenesis of systemic mastocytosis (SM). Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, KIT and ABL kinase activity.

Mechanism of action

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.

Clinical trials

Clinical studies in Chronic Myeloid Leukaemia (CML)

One large, open-label, multicentre, international randomised Phase III study has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML). Three international, open-label, single-arm studies have also been conducted in patients with Ph+ CML: 1) in the chronic phase after failure of interferon-alfa (IFN) therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. In the open-label studies, about 45% of patients were women and 6% were black, 38-40% of patients were ≥ 60 years of age and 10-12% of patients were ≥ 70 years of age. In addition, children have been treated in two phase I studies.

Chronic phase, newly diagnosed (Study 0106)

This phase III study compared treatment with either single-agent Glivec or a combination of interferon-alfa (IFN) plus cytarabine (Ara-C). The main inclusion criteria were: patients aged between 18 and 70 years, diagnosis of chronic phase CML within the previous 6 months, presence of Philadelphia chromosome or variants on cytogenetic analysis, no previous treatment except hydroxyurea or anagrelide. Patients who had failed bone marrow transplantation or who had residual leukaemia after transplantation were excluded from the study. Patients showing lack of response [lack of complete haematological response (CHR) at 6 months, increasing white blood cell count (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. In the Glivec arm, patients were treated with 400 mg daily. In the IFN+Ara-C arm, patients were treated with a target dose of IFN of 5 MIU/m²/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m²/day for 10 days/month.

A total of 1106 patients were randomised from 177 centres in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18-70 years), with 21.9% of patients ≥ 60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% black patients. At the cut-off for this analysis (7 years after the last patient had been recruited), the median follow-up for all patients was 82 and 80 months in the Glivec and IFN+Ara-C arms, respectively. 60% of patients randomised to Glivec are still receiving first-line treatment. In these patients, the average dose of Glivec was 403 \pm 57 mg. The median duration of second-line treatment with Glivec was 64 months. As a consequence of a higher rate of

both discontinuations and crossovers, only 2% of patients randomised to IFN+Ara-C are still on first-line treatment. In the IFN+Ara-C 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 was 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, haematological 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 10.

Table 10. Response in newly diagnosed CML Study (84-month data)

	Glivec	IFN+Ara-C
(Best response rates)	N=553	N=553
Haematological response¹		
CHR rate - n (%)	534 (96.6)*	313 (56.6)*
[95% CI]	[94.7, 97.9]	[52.4, 60.8]
Cytogenetic response²		
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 response³		
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

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

WBC < 10 x10⁹/L, platelet < 450 x10⁹/L, myelocyte+metamyelocyte < 5% in blood, no blasts and promyelocytes in blood, basophils < 20%, no extramedullary involvement

²**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.

³**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 standardised baseline.

Rates of complete haematological response, major cytogenetic response and complete cytogenetic response on first-line treatment were estimated using the Kaplan-Meier approach, for which non-responses were censored at the date of last examination. Using this approach the estimated cumulative response rates for first-line treatment with Glivec are shown in Table 11.

Table 11. Estimated cumulative responses to first-line Glivec

Months on therapy	%CHR	%MCyR	%CCyR
12 months	96.4	84.6	69.5
24 months	97.2	89.5	79.7
36 months	97.2	91.1	83.6
48 months	98.2	91.9	85.2
60 months	98.4	91.9	86.7
84 months	98.4	91.9	87.2

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

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% [90,95] versus 85.1% [82,89], $p < 0.001$) (Figure 2). The annual rate of progression decreased with time on therapy: yearly rates of disease progression to accelerated phase or blast crisis were 1.5%, 2.8%, 1.6%, 0.9%, 0.5%, 0% and 0.4% in the first to seventh year, respectively.

Figure 1. Time to progression (ITT principle)

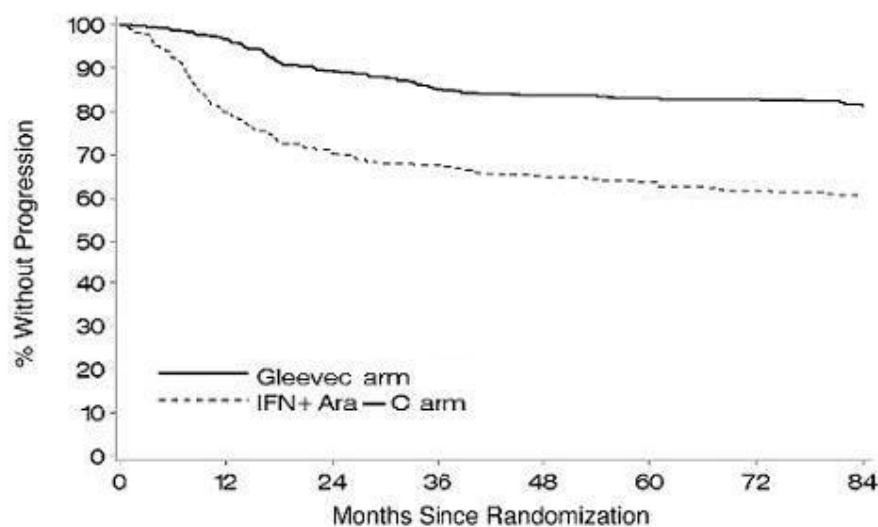
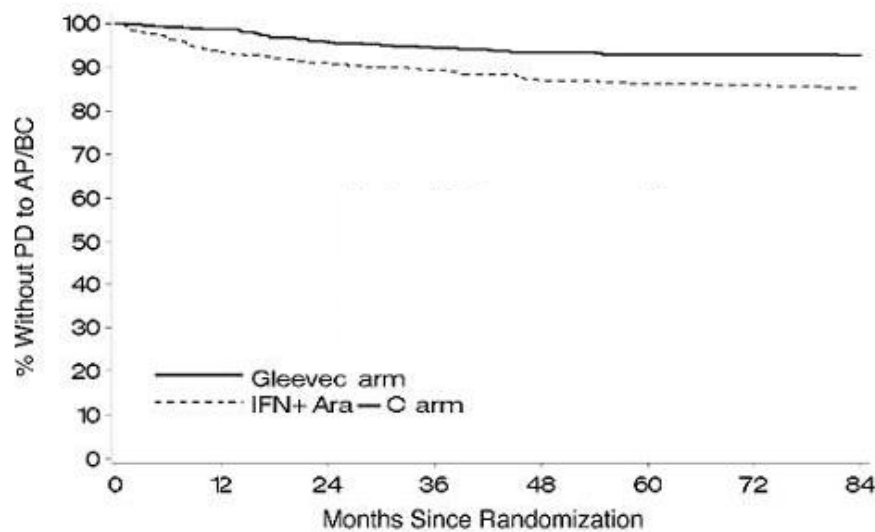


Figure 2. Time to progression to Accelerated Phase or Blast Crisis (ITT principle)



A total of 71 (12.8%) and 85 (15.4%) patients died in the Gleevec and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80, 87) in the randomised Gleevec 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 Gleevec. Additionally, a greater number of patients received bone marrow transplant (BMT) after discontinuation of study treatment in the IFN+Ara-C group ($n=66$, 38 after crossover to Gleevec) compared with the Gleevec group ($n=50$, 8 after crossover to IFN) at the 84 month update. 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 Gleevec 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). The effect of Gleevec treatment on survival in chronic phase, newly diagnosed CML has been further examined in a retrospective analysis of the above reported Gleevec data with the primary data from another Phase III study using IFN+Ara-C ($n=325$) in an identical regimen. In this publication, the superiority of Gleevec over IFN+Ara-C in overall survival was demonstrated ($p<0.001$); within 42 months, 47 (8.5%) Gleevec patients and 63 (19.4%) IFN+Ara-C patients had died.

The degree of cytogenetic response had a clear effect on long-term outcomes in patients on Gleevec. Whereas an estimated 96% (93%) of patients with CCyR (PCyR) at 12 months were free of progression to AP/BC at 84 months, only 81% of patients without MCyR at 12 months were free of progression to advanced CML at 84 months ($p<0.001$ overall, $p = 0.25$ between CCyR and PCyR). Based on the 18-months landmark, the estimates were 99%, 90% and 83% respectively, now also including a statistically significant difference between CCyR and PCyR ($p<0.001$).

Molecular monitoring represented important additional prognostic information. For patients with CCyR and reduction in BCR-ABL transcripts of at least 3 logarithms at 12 months, the probability of remaining progression free at 60 months was numerically greater when compared to patients who had CCyR but less than 3 log reduction (95% vs. 89%, $p=0.068$), and significantly greater than that observed for patients who were not in CCyR at 12 months (70%, $p<0.001$). Considering only

progression to AP/BC, the estimated rates without event were 100%, 95% and 88% respectively ($p < 0.001$ overall, $p = 0.007$ between CCyR with and without MMR). Using the 18 months landmark, the estimated rates without AP/BC at 60 months were 100% for patients with CCyR and MMR, 98% for patients with CCyR but without MMR and only 87% for patients without CCyR ($p < 0.001$ overall, $p = 0.105$ between CCyR with and without MMR).

Quality of Life was measured using the validated FACT-BRM instrument. All domains were assessed and reported significantly higher scores in the Glivec arm compared to the IFN arm. QoL data showed that patients maintain their well being while on treatment with Glivec.

Escalation of the Glivec dose to 600 mg per day was allowed in patients satisfying one of the following criteria:

- No CHR after 3 months
- No minor cytogenetic response ($>65\%$ Ph+) after 12 months or
- Confirmed loss of MCyR (increase in Ph+ bone marrow cells by at least 30 percentage points e.g. from 20% to 50% or from 30% to 60%) confirmed by a second cytogenetic analysis ≥ 1 month later.

If toxicity was no greater than mild during the initial 4 weeks on 600 mg per day, then further dose escalation to 800 mg per day was allowed.

It should be noted, however, that some patients in the above categories eventually responded to Glivec without need for dose escalation. The small number of patients who received a higher dose achieved proportionately more cytogenetic responses (Table 12). Dose escalation was associated with an increased incidence of adverse reactions including gastrointestinal haemorrhage, elevation of serum bilirubin and transaminases and conjunctivitis.

Table 12. Efficacy of Glivec Dose Escalation

Criterion	No Dose Increase		Increase to 600 mg ¹		Increase to 800 mg ²	
	N	Response (%)	N	Response (%)	N	Response (%)
No CHR at 3 months	55	44 CHR (80%)	2	1 CHR (50%)	6	3 CHR (50%)
No Min CyR at 12 months	37	9 CCyR, 3 PCyR (32%)	4	1 CCyR, 2 PCyR (75%)	5	1 CCyR, 1 PCyR (40%)
Loss of conf. MCyR	7	1 MCyR (14%)	0	-	4	2 MCyR (50%)

¹ For ≥ 28 days – includes patients who spent <28 days on 800 mg/day. ² For ≥ 28 days.

CCyR: Complete CyR, PCyR: Partial CyR

Chronic phase, prior interferon-alfa treatment (Study 0110)

532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon-alfa: failure to achieve (within 6 months) or loss of a complete haematological response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon-alfa (36%). Patients had received a median of 14 months of prior IFN therapy at doses $\geq 25 \times 10^6$ IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of haematological response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Efficacy results are reported in Table 13. Results were similar in the three subgroups described above.

Accelerated phase (Study 0109)

235 patients with accelerated phase disease were enrolled. These patients met one or more of the following criteria: $\geq 15\%$ - $<30\%$ blasts in PB or BM; $\geq 30\%$ blasts + promyelocytes in PB or BM; $\geq 20\%$ basophils in PB; $<100 \times 10^9/L$ platelets. The first 77 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

Effectiveness was evaluated primarily on the basis of the rate of haematological response, reported as either complete haematological response, no evidence of leukaemia (i.e. clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses) or return to chronic phase CML. Cytogenetic responses were also evaluated. Efficacy results are reported in Table 13. Haematological and major cytogenetic responses were more frequent for patients receiving 600 mg Glivec daily than for those receiving 400 mg daily (75% vs 65% and 32% vs 19%, respectively). In accelerated phase, median duration of haematological response for the 400 mg group is 17 months, whereas it is 30.7 months for the 600 mg group ($p=0.0027$). For the patients treated at 600 mg, the current estimates for median progression-free survival and overall survival are 22.9 and 42.5 months, respectively.

Myeloid blast crisis (Study 0102)

260 patients with myeloid blast crisis were enrolled. These patients had $\geq 30\%$ blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pre-treated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg; the remaining 223 patients were started at 600mg.

Effectiveness was evaluated primarily on the basis of rate of haematological response, reported as either complete haematological response, no evidence of leukaemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic responses were also assessed. Efficacy results are reported in Table 13. The haematological response rate was higher in untreated patients than in treated patients (36% and 22%, respectively; $p=0.0255$) and in the group receiving an initial dose of 600 mg than 400 mg (33% and 16%, respectively; $p=0.053$).

Table 13. Response in CML patients in Studies 0110, 0109 and 0102

	Study 0110 Chronic phase, IFN failure (N=532) 400 mg	Study 0109 Accelerated phase (N=235) 600 mg N=158 400 mg N=77	Study 0102 Myeloid blast crisis (N=260) 600 mg N=223 400 mg N=37
Treated for more than 24 months	81%	45%	10%
	% of patients (CI _{95%})		
Haematological response ¹	95% (92.3-96.3)	71% (65.3-77.2)	31% (25.2-36.8)
Complete haematological response (CHR)	95 %	42 %	8 %
No evidence of leukaemia (NEL)	Not applicable	12 %	5 %
Return to chronic phase (RTC)	Not applicable	17 %	18 %
Median time to haematological response	1 month	1 month	1 month

Estimated % still in haematological response after 24 months	72%	40% (400 mg) 61% (600 mg)	28%
Major cytogenetic response ²	65% (61.2-69.5)	28% (22.0-33.9)	15% (11.2-20.4)
Complete(confirmed ³)	53% (43%)	20 (16%)	7% (2%)
Estimated % progression-free at 24 months	85%	33% (400 mg) 50% (600 mg)	NA
Estimated % alive at 24 months	91%	46% (400 mg) 66% (600 mg)	18%

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

CHR: chronic phase study [WBC <10 x10⁹/L, platelets <450 x10⁹/L, myelocytes+metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x10⁹/L, platelets ≥100 x10⁹/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: Same criteria as for CHR but ANC ≥1 x10⁹/L and platelets ≥20 x10⁹/L (accelerated and blast crisis studies)

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

BM=bone marrow, PB=peripheral blood

²Cytogenetic response criteria:

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

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

Efficacy results were similar in men and women and in patients younger and older than age 65.

Responses were seen in black patients, but there were too few black patients to allow a quantitative comparison.

Paediatric patients

A total of 51 paediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicentre, single arm phase II trial and were treated with Glivec 340 mg/m²/day. Glivec treatment induced a rapid response in newly diagnosed paediatric 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.

In an uncontrolled trial, 14 children with chronic phase CML were treated with imatinib following relapse after stem cell transplantation or resistance to interferon. After excluding 2 children with minimal disease at study entry and another with no cytogenetic data, 6 children (55%) had complete cytogenetic responses and 3 (27%) had major responses. The children were aged 8-20 years with 5 males and 6 females. By dose, the complete response rates were 67% (2 out of 3), 67% (2 out of 3), 33% (1 out of 3) and 50% (1 out of 2) for the 260, 340, 440 and 570 mg/m² doses respectively. Median follow-up time was 17 months. There are insufficient data to suggest that the lowest dose (260 mg/m²) differs in efficacy compared with the higher doses.

The trial also enrolled 4 children with blast crisis (aged 3-18 years, 3 male), but none with accelerated phase CML. Two children were dosed at 260 mg/m², one at 340 mg/m² and one at 570 mg/m². Based on the criterion of < 5% blasts in bone marrow, neither of the two children treated at 260 mg/m² responded, but the children treated at the higher doses did. The child treated at 340 mg/m² achieved a major cytogenetic response. There were no complete responses. The data supports the dose recommendation of 340 mg/m² for children with blast crisis.

In another uncontrolled trial, there were 3 children with chronic phase CML and one with CML in blast crisis. The 3 chronic phase children (aged 5-13 years, 2 male) received imatinib doses of 200, 242 and 258 mg/m². Complete cytogenetic responses were achieved in 2 of the 3 children (doses 242, 258 mg/m²). The child with blast crisis, a boy aged 7 years, was treated at 362 mg/m² and achieved a complete cytogenetic response.

Clinical Studies in Acute Lymphoblastic Leukaemia (Ph+ALL)

A total of 851 Ph+ ALL patients with either newly diagnosed or relapsed/refractory disease were enrolled in eleven clinical studies, ten were uncontrolled and one was randomized. Of the 851 patients, 93 were paediatric 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: Imatinib monotherapy (600 mg per day) as induction was tested in a randomised, controlled study versus chemotherapy (GMALL protocol for elderly patients) in 55 newly diagnosed patients aged 55 years and over. Used as a single agent, imatinib (N= 28) resulted in a significantly higher CHR than chemotherapy (N=27) (96.3% vs. 50%; p=0.0001) in the induction phase. When salvage therapy with imatinib was used in patients who did not respond or who responded poorly to induction with chemotherapy, it resulted in 9 (81.8%) out of 11 patients achieving a CHR. This clinical effect was associated with a greater reduction in BCR-ABL transcripts in the imatinib-treated patients than in the chemotherapy arm after 2 weeks of therapy (p=0.02). Following induction, all patients received imatinib (600 mg/day) combined with consolidation chemotherapy and the levels of BCR-ABL transcripts were comparable in the two arms at 8 weeks. Since patients received the same treatment in both arms after the induction phase, it was expected and observed that there was no difference in remission duration, disease-free survival or overall survival. However, it was observed that 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).

Three studies compared chemotherapy regimens integrating imatinib with historical data of chemotherapy alone.

In study AUS01 imatinib (400 mg/day on days 1 – 14 of each chemotherapy cycle during induction/consolidation, and 600 mg daily during maintenance treatment) was integrated into a HyperCVAD chemotherapy protocol, in Ph+ ALL patients with *de novo* disease (N=21), disease refractory to one cycle chemotherapy (N=5) or patients with a complete response after 1 cycle of chemotherapy (N=6). Results are summarized in the following table:

	Imatinib + HyperCVAD	HyperCVAD alone (historical data)	p value
N	32	50	
Complete Response	96%	94%	NS
Disease-free survival at 2 years	87%	28%	< 0.001

In study AJP01 imatinib (600 mg/day on days 8 – 63 of induction chemotherapy, and on days 1 – 28 of each chemotherapy cycle during consolidation and maintenance) was integrated into a chemotherapy regimen in 80 patients with *de novo* Ph+ ALL. Results are summarized in the following table:

	Imatinib + Chemotherapy	Chemotherapy alone (historical data)	p value
N	80	51	
Complete Response	96%	51%	NS

Analysis of event-free survival and overall survival also indicated superiority of the imatinib-containing regimen ($p < 0.0001$ for both).

In study AFR-09 imatinib (600 mg/day for two months during consolidation/salvage chemotherapy, and for two separate two-month periods during maintenance chemotherapy) was integrated into a chemotherapy regimen in 30 patients aged > 55 years with *de novo* Ph+ ALL. Results are summarized in the following table:

	Imatinib + Chemotherapy	Chemotherapy alone (historical data)	p value
N	30	21	
Complete Response after consolidation / salvage	90%	48%	= 0.001
Relapse-free survival at 1 year	59%	11%	= 0.001
Overall survival at 1 year	68%	43%	= 0.001

Paediatric patients: In study I2301, a total of 93 paediatric, adolescent and young adult patients (2 patients were < 2 years, 52 patients were from 2 to < 12 years, 32 patients were from 12 to < 18 years and 6 patients were from 18 to < 22 years) with Ph+ ALL were enrolled between 2002 and 2006 in an open-label, multicentre, sequential cohort, nonrandomised phase III trial, and were treated with Glivec (340 mg/m²/day) in combination with intensive chemotherapy after initial induction therapy. Glivec was administered intermittently in cohorts 1-5, 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 and intermittent schedule of Glivec 2 weeks every 4 weeks only during the last eight maintenance cycles). 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 (enrolled between 1988 and 1995).

Patients with (human leukocyte antigen (HLA)-matched related donors or 1 antigen mismatched (excluding HLA)-DR mismatch) related donors were eligible for HSCT on study after Consolidation block 2 (per protocol HSCT). At 16 to 24 weeks after per protocol HSCT, treatment with imatinib was resumed, initially at a lower dose of 230 mg/m²/day and increased to 340 mg/m²/day when no toxicities (\geq grade 3) were observed after 4 weeks of post-HSCT imatinib. The total duration of imatinib treatment post-HSCT was 24 weeks.

Relapsed/refractory Ph+ ALL: A total of 429 patients with relapsed/refractory Ph+ALL or CML blast crisis were enrolled in three studies assessing the efficacy and safety of imatinib as monotherapy.

Imatinib was given as single agent in 66 patients evaluable for efficacy and resulted in a haematological response rate of 33% (12% of which were complete) and a MCyR rate of 23%. The median time to progression for the overall population of 429 patients with relapsed/refractory Ph+ ALL ranged from 1.9 to 3.1 months, and median overall survival for the 409 evaluable patients ranged from 5 to 9 months.

Of the 429 patients described above, 146 were ≥ 55 years of age. The median time to progression and overall survival in this sub-population was similar to the overall population.

Clinical Studies in myelodysplastic/myeloproliferative diseases (MDS/MPD) expressing imatinib-sensitive kinases

One open label, multinational, multicentre, phase II clinical trial (study B2225) was conducted testing Glivec in diverse populations of patients suffering from very rare and 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 haematological diseases and 140 a variety of solid tumours. These patients were treated with Glivec 400 mg daily, with provision to increase to 800 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 400mg 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 haematological 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 haematologically (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 haematological 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 (RT-PCR negative for PDGFR β fusion oncogene). Median duration of therapy was 12.9 months (0.8 - 26.7) in the 7 patients treated within study B2225 and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in table 14.

Table 14. Response in MDS/MPD

	N	Complete haematological response(%)	Cytogenetic response(%)
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. Patient responded molecularly to treatment (RT-PCR negative for PDGFR β fusion oncogene)

Clinical Studies in aggressive systemic mastocytosis (ASM)

Study B2225 also included 5 patients with ASM out of a total of 185 patients enrolled. The ASM patients were treated with Glivec 100 mg to 400 mg daily, with provision to increase the dose to 800 mg daily. The ages of these patients ranged from 49 to 74 years. A further 25 patients with ASM aged 26 to 85 years were reported in 10 published case reports and case series. These patients also received Glivec at doses of 100 mg to 400 mg daily. Of the total population of 30 patients treated for ASM, 10 (33%) achieved a complete haematological response and 9 (30%) a partial haematological response (63% overall response rate). Cytogenetic abnormalities were evaluated in 21 of the 30 patients treated. Eight out of these 21 patients had FIP1L1-PDGFR α fusion kinase. Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their systemic mast cell disease. Two patients showed a KIT mutation in the juxtamembrane 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 reported in the reviewed literature with the D816V c-KIT mutation were not considered sensitive to Glivec. Median duration of therapy was 13 months (range 1.4 to 22.3 months) in the 5 patients treated within study B2225 and ranged between 1 month and more than 30 months in responding patients in the published literature. Results are provided in Table 15.

Table 15. Response in ASM

Cytogenetic abnormality	N	Complete haematological response	Partial haematological response
FIP1L1-PDGFR α fusion kinase (or CHIC2 deletion)	8	8	0
Juxtamembrane 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

Glivec has not been shown to be effective in patients with less aggressive forms of systemic mastocytosis. Glivec is not recommended for use in patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), SM with an associated clonal haematological non-mast cell lineage disease, mast cell leukaemia, mast cell sarcoma or extracutaneous mastocytoma. *In vitro*, cell lines and patient-derived mast cells harbouring the KIT D816V mutation were resistant to imatinib and the effectiveness of Glivec in the treatment of patients with SM who have the D816V mutation remains controversial.

Clinical studies in hypereosinophilic syndrome and/or chronic eosinophilic leukaemia (HES/CEL)

Study B2225 also included 14 patients with HES/CEL out of a total of 185 patients enrolled. These patients were treated with 100 mg to 1,000 mg of Glivec daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series with a cut-off date of 15-Jan-06. These patients received Glivec at doses of 75 mg to 800 mg daily. Of the total population of 176 patients treated for HES/CEL,

107 (61%) achieved a complete haematological response and 16 (9%) a partial haematological response (70% overall response rate). Cytogenetic abnormalities were evaluated in 117 of the 176 patients treated. Out of these 117 patients, 61 were positive for FIP1L1-PDGFR α fusion kinase. All these FIP1L1-PDGFR α fusion kinase positive patients achieved a complete haematological response. The FIP1L1-PDGFR α fusion kinase was either negative or unknown in 115 patients, of which 62 (54%) achieved either a complete (N=46) or partial (N=16) haematological response. Results are provided in Table 16.

Table 16. Response in HES/CEL

Cytogenetic abnormality	N	Complete haematological response	Partial haematological response
Positive FIP1L1-PDGFR α fusion kinase	61	61	0
Negative FIP1L1-PDGFR α fusion kinase	56	12	9
Unknown cytogenetic abnormality detected	59	34	7
Overall totals	176	107 (61%)	16 (9%)

Additionally, improvements in symptomatology and other organ dysfunction abnormalities were reported by the investigators in the case reports. Improvements were reported in cardiac, nervous, skin/subcutaneous tissue, respiratory/thoracic/mediastinal, musculoskeletal/connective tissue/vascular, and gastrointestinal organ systems.

Clinical studies in unresectable or metastatic Gastrointestinal Stromal Tumours (GIST)

Two open-label, randomised, multinational Phase III studies (SWOG, EORTC) were conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumours (GIST). The design of these two studies were similar allowing a predefined combined analysis of safety and efficacy. A total of 1,640 patients were enrolled into the two studies and randomized 1:1 to receive either 400 mg or 800 mg orally q.d. continuously until disease progression or unacceptable toxicity. Patients in the 400 mg q.d. treatment group who experienced disease progression were permitted to crossover to receive treatment with 800 mg q.d. The studies were designed to compare response rates, progression free survival and overall survival between the dose groups. Median age at patient entry was 60 (range 17 to 94, 25th-75th age percentile 50 to 69). Males comprised 58% of the patients enrolled. All patients had a pathologic diagnosis of CD117 positive unresectable and/or metastatic malignant GIST.

The primary objective of the EORTC study was to evaluate progression free survival (PFS) with a secondary objective to evaluate overall survival (OS) The primary objective of the SWOG trial was to evaluate OS with a secondary objective, PFS. A planned analysis of both OS and PFS from the combined datasets from these two studies was conducted. Neither study showed an advantage for the higher daily dose of 800 mg, so the data from both trials were pooled. No benefit of the higher dose was seen in OS or in Best Overall Tumour Response rates from the analysis of the pooled data, but a statistically significant increase in PFS was shown (Table 17).

Table 17. Overall survival, Progression Free Survival and Tumour 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) [95% CI]	18.9 [17.4-21.2]	23.2 [20.8-24.9]	21.0 [19.4-22.5]
Overall Survival (months) [95% CI]	49.0 [45.3-60.0]	48.7 [45.3-51.6]	48.8 [46.3-51.6]
Best Overall Tumour 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 (25th – 75th percentile 19 to 46 months). There was a statistically significant improvement in PFS in the 800 mg treatment group (23.2 months [95% CI, 20.8 to 24.9]) compared to the 400 mg treatment group (18.9 months [95% CI, 17.4 to 21.2]) (p=0.03). However, there were no observed differences in overall survival between the treatment groups (p=0.98). The estimated overall PFS for all 1640 patients in these Phase III studies was 21 months [95% CI 19.4 to 22.5] and the estimated OS of 48.8 months [95% CI 46.3 to 51.6]. 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.

Patients who crossed over following disease progression from the 400 mg/day treatment group to the 800 mg/day treatment (N=347) had a 3.4 month median and 7.7 month mean exposure to Glivec following crossover. Overall survival of patients following crossover was 14.3 months [95% CI 12.2 to 16.7] and 19.3% of these patients were still alive at 48 months.

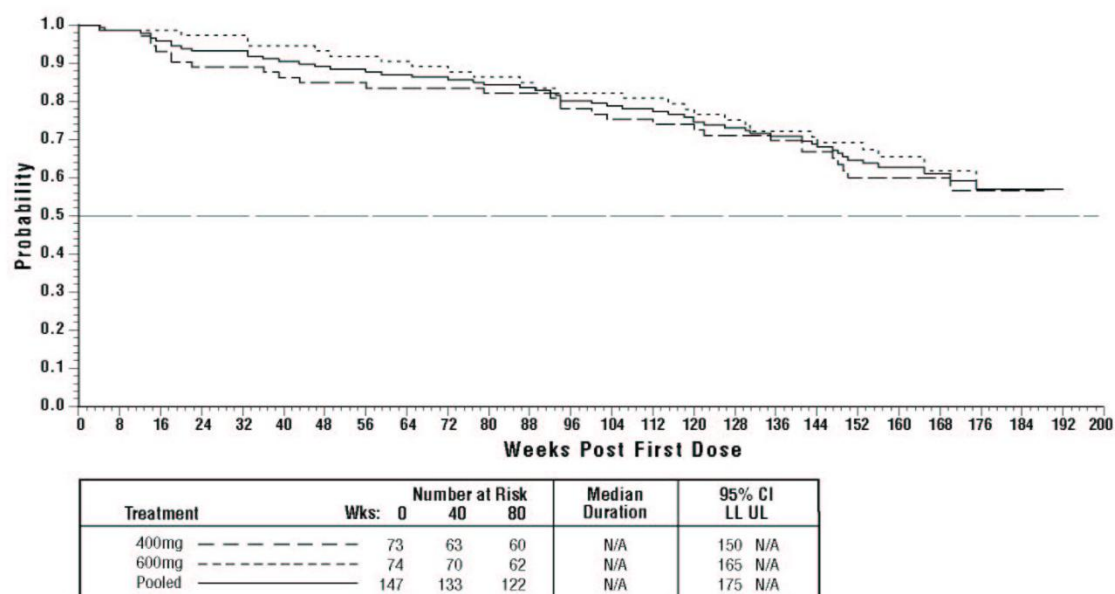
One phase II, open-label, randomised multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumours (GIST). In this study 147 patients were enrolled and randomised to receive either 400 mg or 600 mg Glivec orally daily for up to 36 months. These patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of KIT-positive malignant GIST that was unresectable and/or metastatic.

The primary evidence of efficacy was based on objective response rates. Tumours were required to be measurable in at least one site of disease and response characterisation 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 18.

Table 18. Tumour response in GIST

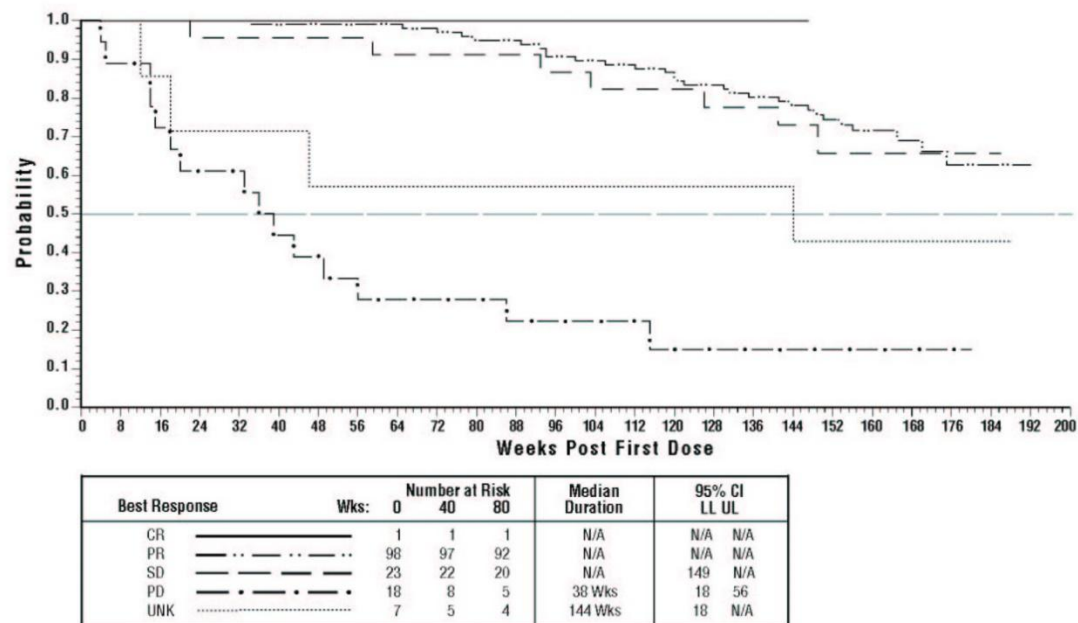
Total Patients	N	Confirmed Partial Response, N (%)	95% Confidence Interval
400 mg daily	73	49 (67.1%)	55.1%, 77.7%
600 mg daily	74	49 (66.2%)	55.6%, 78.0%
Total	147	98 (66.7%)	59.1%, 74.8%

A statistically significant difference in response rates between the two dose groups was not demonstrated. A significant number of patients who had stable disease at the time of the interim analysis achieved a partial response with longer treatment (median follow-up 31 months). Median time to response was 13 weeks (95 % C.I. 12 to 23). Median time to treatment failure in responders was 122 weeks (95% C.I. 106 to 147), while in the overall study population it was 84 weeks (95% C.I. 71 to 109). The median overall survival has not been reached. The Kaplan-Meier estimate for survival after 36-month follow-up is 68 % [Figure 3]. Additionally, there is no difference in survival between patients achieving stable disease and partial response [Figure 4].

Figure 3. Kaplan-Meier estimate of overall survival since start of study by treatment

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

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



Clinical studies in adjuvant GIST

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

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.

In the planned interim analysis at a median follow-up of 15 months in patients without an RFS event, Glivec significantly prolonged RFS compared to placebo (hazard ratio 0.40, 95% CI [0.26, 0.61], $p < 0.0001$). After the interim analysis of RFS, 72 of the 354 patients randomized to placebo crossed over to one year of Glivec. In an updated analysis of 50 months median follow-up in patients without an event, the hazard ratio for RFS remained significant at 0.72, 95% CI: [0.53, 0.97]. At 61 months median survival follow-up (measured in patients still alive), the hazard ratio for overall survival (OS) was not significant but favoured Glivec: 0.82, 95% CI: [0.49, 1.37]. Death due to any cause was reported in 26 patients on Glivec (11 due to GIST) and 33 patients on placebo (18 due to GIST). An OS analysis censoring placebo patients eligible for cross-over to Glivec was also not significant but supportive of Glivec: HR=0.75; 95% CI: [0.44, 1.26].

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 KIT-positive GIST and one of the following: tumour diameter >5 cm and mitotic count >5/50 high power fields (HPF); or tumour diameter >10 cm and any mitotic count or tumour of any size with mitotic count >10/50 HPF or tumours 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 19, Figure 5). 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 19, Figure 6). The total number of deaths were 25 for the 12-months treatment arm and 12 for the 36-months treatment arm. Three randomized patients (one from 12-month group and two from the 36-month group) did not give informed consent and were excluded from analysis.

Table 19. 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 5. Kaplan-Meier estimates for primary recurrence-free survival endpoint (ITT population)

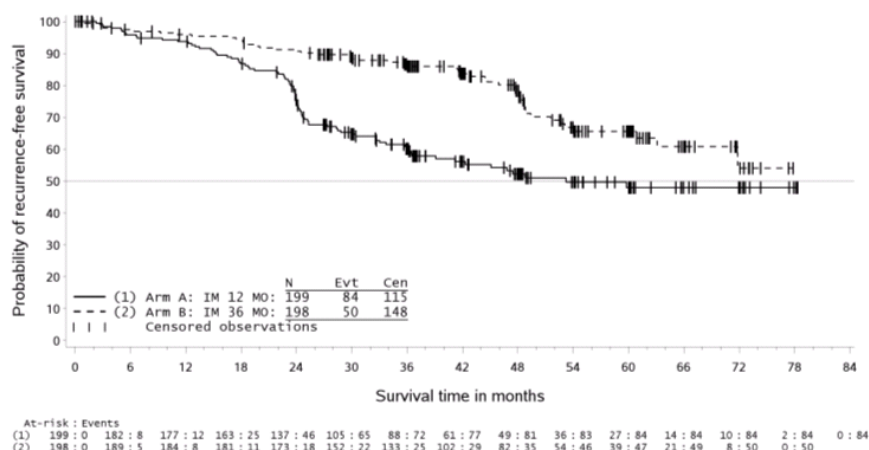
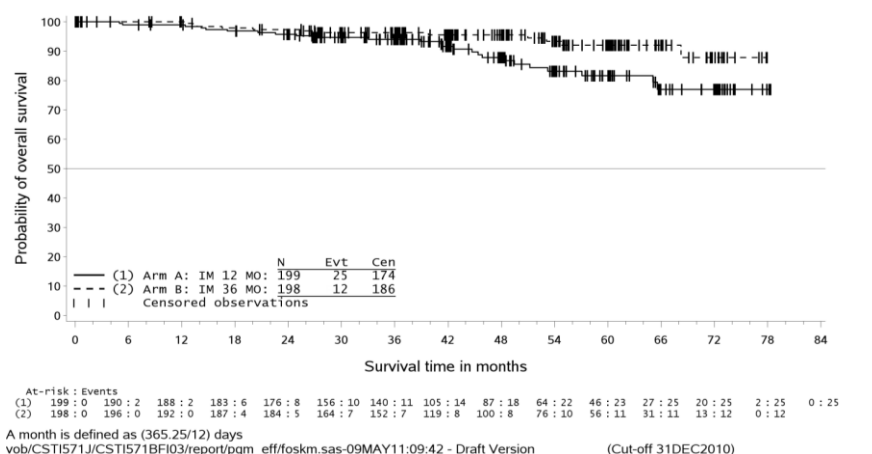


Figure 6. Kaplan-Meier estimates for overall survival (ITT population)



Clinical studies in dermatofibrosarcoma protuberans (DFSP)

Study B2225 (see section 5.1 Pharmacodynamic properties - Clinical studies in MDS/MPD expressing imatinib-sensitive kinase) also included 12 patients with DFSP out of a total of 185 patients. The primary evidence of efficacy for patients in the solid tumour group (N=140) was based on objective response rates. The solid tumour 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 were 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 paediatric patient received 400 mg/m²/daily, subsequently increased to 520 mg/m²/daily. Responses to treatment are described in Table 20.

Table 20. Response rate in 18 DFSP patients treated with imatinib

Tumour 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.

The effectiveness of Glivec is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL, SM, and progression-free survival in unresectable and/or metastatic and objective response rates in GIST, on recurrence free survival in adjuvant GIST, and on objective response rates in DFSP. There are no controlled trials demonstrating increased survival.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of Glivec have been evaluated over a dosage range of 25 to 1000 mg. Plasma pharmacokinetic profiles were analysed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

Absorption

Imatinib is well absorbed after oral administration, with maximum plasma concentrations (C_{\max}) being reached approximately 2 hours after dosing. 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.

The increase in AUC was linear and dose proportional in the range of 25-1000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5–2.5-fold at steady state when dosed once daily. Plasma concentrations of imatinib and its main metabolite showed significant inter-subject variability.

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. The volume of distribution is about 435 L.

Metabolism

Imatinib is cleared from plasma predominantly by metabolism and CYP 3A4 is the main enzyme responsible. In healthy volunteers, clearance is approximately 14 L/hr and the drug has a half-life of approximately 18 hours, suggesting that once-daily dosing is appropriate.

The main circulating metabolite in humans is the N-demethylated piperazine derivative, which shows similar *in vitro* potency as imatinib. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. Its half-life was approximately 40 hours. The plasma protein binding of the N-demethylated metabolite is similar to that of imatinib.

Imatinib competitively inhibits CYP2C9, CYP2D6 and CYP3A4/5, with K_i values indicating that CYP2D6 and CYP3A4-dependent metabolism of concomitantly administered drugs may be reduced (see section 4.5 Interactions with other medicines and other forms of interactions).

Excretion

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

Pharmacokinetics in special patient groups

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. 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.

The effect of body weight on the clearance of imatinib is such that for a 50 year old patient weighing 50 kg the mean clearance is expected to be 8 L/h, while for a 50 year old patient weighing 100 kg the clearance will rise to 14 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.

Pharmacokinetics in children

As in adult patients, imatinib was rapidly absorbed after oral administration in children in both Phase I and II studies, with a C_{max} of 2-4 hours. Apparent oral clearance was also similar (mean 11.0 L/h/m² in children vs. 10.0 L/h/m² in adults) as was half-life (mean 14.8 h in children vs. 17.1 h in adults). Dosing in children at both 260 mg/m² and 340 mg/m² achieved an AUC similar to a 400 mg and 600 mg dose, respectively, in adults. After repeated once daily dosing at 260 mg/m² and 340 mg/m², drug accumulation was 1.5 and 2.2-fold respectively, on comparing AUC_{0-24h} on days 1 and 8. Mean imatinib AUC did not increase proportionally with increasing dose.

Based on pooled population pharmacokinetic analysis in paediatric patients with haematological disorders (CML, Ph+ALL, or other haematological 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 paediatric 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. No pharmacokinetic data have been obtained in children < 2 years of age.

Pharmacokinetics in patients with impaired renal or hepatic function

In a study of patients with varying degrees of hepatic dysfunction (mild, moderate and severe – see table below for classification of these terms), the mean exposure to imatinib (dose normalised AUC)

showed similar exposure between patients with mild and moderate impairment, but an approximately 45% higher exposure in patients with severe impairment. In this study, 500 mg daily was safely used in patients with mild liver impairment 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 impairment, pharmacokinetic analysis projects that 400 mg can be used safely in patients with moderate liver impairment, and a dose of 300 mg can be used for patients with severe liver impairment. (See section 4.4 Special warnings and precautions for use, section 4.8 Adverse effects (Undesirable effects) and section 4.2 Dose and method of administration). Glivec should be used with caution in patients with liver impairment. (See section 4.4 Special warnings and precautions for use).

Liver function classification

Liver dysfunction	Liver function tests
Mild	Total bilirubin: = 1.5 ULN AST: > ULN (can be normal or < ULN if total bilirubin is > ULN)
Moderate	Total bilirubin: > 1.5-3.0 ULN AST: any
Severe	Total bilirubin: > 3-10 ULN AST: any

ULN= upper limit of normal for the institution

AST = aspartate aminotransferase

Imatinib and its metabolites are not excreted via the kidney to a significant extent. In a study of patients with varying degrees of renal dysfunction (mild, moderate and severe - see table 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 haemodialysis 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 haemodialysis. 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 section 4.4 Special warnings and precautions for use and section 4.2 Dose and method of administration).

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

5.3 PRECLINICAL SAFETY DATA

In mice *in vivo*, imatinib inhibits tumour growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukaemia cell lines derived from CML patients.

Toxicities from long-term use

Liver toxicity was observed in the 3 species tested in repeated-dose studies (rats, dogs and cynomolgus monkeys), and was most severe in dogs, in which findings included elevated liver enzymes, hepatocellular necrosis, and bile duct necrosis and hyperplasia.

Renal toxicity was observed in rats and monkeys, being most marked in the latter, with increases in blood urea nitrogen (BUN) and creatinine being observed in several animals, and with findings including renal tubular dilatation, mineralisation and nephrosis. Lymphoid tissue atrophy was observed in many of the repeated-dose animal studies and lymphopenia was sometimes observed in animals (as in humans). In a 39-week monkey study, treatment with imatinib apparently resulted in worsening of malarial infections which were normally suppressed in these animals. (See section 4.4 Special warnings and precautions for use)

Genotoxicity

Positive genotoxic effects were observed for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation, but imatinib was negative in an *in vivo* rat micronucleus assay. Imatinib was not genotoxic when tested in assays for gene mutations (*in vitro* bacterial cell assay and an *in vitro* mouse lymphoma assay). Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay.

Carcinogenicity

In a 2-year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in neoplastic changes in 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 glands.

The 30 mg/kg/day dose in rats is approximately equivalent to the human daily exposure (based on plasma AUC) at 800 mg/day and 2 times the daily exposure in children (based on AUC) at 340 mg/m².

These findings are potentially relevant for patients receiving long-term imatinib therapy. However, 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, or the incidence of bladder,

kidney or prostate tumours in patients treated with imatinib compared to that of the general population.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets: cellulose-microcrystalline, crospovidone, hypromellose, silica colloidal anhydrous, magnesium stearate, iron oxide yellow CI 77492, iron oxide red CI77491, macrogol 4000, talc

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Glivec 100 mg film-coated tablet: Store in the original package below 30°C and protect from moisture.

Glivec 400 mg film-coated tablet (PA/Al/PVC blister): Store in the original package below 30°C and protect from moisture.

Keep out of the reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Glivec 100 mg film-coated tablet: Blister packs, PVC/PE/PVDC/Al containing 56, 60, 180 tablets.

Glivec 400 mg film-coated tablet: Blister packs, PA/Al/PVC containing 28, 30 tablets.

Not all presentations/pack sizes are available in Australia.

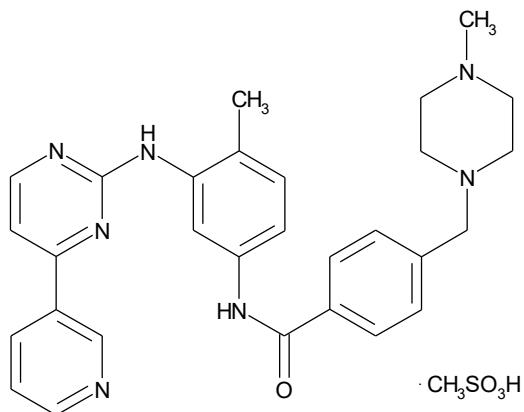
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Imatinib mesilate is a white to slightly yellowish powder. It is freely soluble in water and aqueous buffers \leq pH 5.5 and less soluble in more neutral/alkaline aqueous buffers. In non-aqueous solvents, the compound is soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Chemical structure



Chemical name: 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate

Molecular formula: C₂₉H₃₁N₇O · CH₄SO₃

Molecular weight: 493.6 (free base) + 96.1 (mesilate) = 589.7

CAS number

152459-95-5 (free base); 220127-57-1 (mesilate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

13 August 2001

10 DATE OF REVISION

14 July 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.4, 6.5	Removal of text regarding PVC/PE/PVDC/Al blister pack material for the 400 mg strength

