ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Glivec 100 mg film-coated tablets
Glivec 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glivec 100 mg film-coated tablets

Each film-coated tablet contains 100 mg imatinib (as mesilate).

Glivec 400 mg film-coated tablets

Each film-coated tablet contains 400 mg imatinib (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Glivec 100 mg film-coated tablets

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

Glivec 400 mg film-coated tablets

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

The film-coated tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glivec is indicated for the treatment of

- adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

The effect of Glivec on the outcome of bone marrow transplantation has not been determined.

Glivec is indicated for

- the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, 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 and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with Glivec in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

4.2 Posology 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.

For doses other than 400 mg and 800 mg (see dosage recommendation below), 100 mg and 400 mg divisible tablets are available.

The prescribed dose should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations. 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 still 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).

<u>Posology for CML in adult patients</u>

The recommended dosage of Glivec is 400 mg/day for adult patients in chronic phase CML. Chronic phase CML is defined when all of the following criteria are met: blasts < 15% in blood and bone marrow, peripheral blood basophils < 20%, platelets > 100 x 10^9/l.

The recommended dosage of Glivec is 600 mg/day for adult patients in accelerated phase. Accelerated phase is defined by the presence of any of the following: blasts ≥ 15% but < 30% in blood or bone marrow, blasts plus promyelocytes ≥ 30% in blood or bone marrow (providing < 30% blasts), peripheral blood basophils ≥ 20%, platelets < 100 x 10^9/l unrelated to therapy.

The recommended dose of Glivec is 600 mg/day for adult patients in blast crisis. Blast crisis is defined as blasts ≥ 30% in blood or bone marrow or extramedullary disease other than hepatosplenomegaly.

Treatment duration: In clinical trials, treatment with Glivec was continued until disease progression. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.

Dose increases from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients with accelerated phase or

blast crisis may be considered in the absence of severe adverse drug reaction 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. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for CML in children

Dosing for children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800 mg). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. The dose recommendation is currently based on a small number of paediatric patients (see sections 5.1 and 5.2). There is no experience with the treatment of children below 2 years of age.

Dose increases from 340 mg/m^2 daily to 570 mg/m^2 daily (not to exceed the total dose of 800 mg) may be considered in children in the absence of severe adverse drug reaction 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. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for Ph+ ALL in adult patients

The recommended dose of Glivec is 600 mg/day for adult patients with Ph+ ALL. Haematological experts in the management of this disease should supervise the therapy throughout all phases of care.

Treatment schedule: On the basis of the existing data, Glivec has been shown to be effective and safe when administered at 600 mg/day in combination with chemotherapy in the induction phase, the consolidation and maintenance phases of chemotherapy (see section 5.1) for adult patients with newly diagnosed Ph+ ALL. The duration of Glivec therapy can vary with the treatment programme selected, but generally longer exposures to Glivec have yielded better results.

For adult patients with relapsed or refractory Ph+ALL Glivec monotherapy at 600 mg/day is safe, effective and can be given until disease progression occurs.

Posology for Ph+ ALL in children

Dosing for children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with Ph+ ALL (not to exceed the total dose of 600 mg).

Posology for MDS/MPD

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

Treatment duration: In the only clinical trial performed up to now, treatment with Glivec was continued until disease progression (see section 5.1). At the time of analysis, the treatment duration was a median of 47 months (24 days - 60 months).

Posology for HES/CEL

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

Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if

assessments demonstrate an insufficient response to therapy.

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

Posology for GIST

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

Limited data exist on the effect of dose increases from 400 mg to 600 mg or 800 mg in patients progressing at the lower dose (see section 5.1).

Treatment duration: In clinical trials in GIST patients, treatment with Glivec was continued until disease progression. At the time of analysis, the treatment duration was a median of 7 months (7 days to 13 months). The effect of stopping treatment after achieving a response has not been investigated.

The recommended dose of Glivec is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. Optimal treatment duration is not yet established. Length of treatment in the clinical trial supporting this indication was 36 months (see section 5.1).

Posology for DFSP

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

Dose adjustment for adverse reactions

Non-haematological adverse reactions
If a severe non-haematological adverse reaction develops with Glivec use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, Glivec should be withheld until bilirubin levels have returned to < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with Glivec may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg or from 600 to 400 mg, or from 800 mg to 600 mg, and in children from 340 to 260 mg/m^2/day.

Haematological adverse 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:

HES/CEL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glivec until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD and GIST (starting dose 400 mg) HES/CEL (at dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glivec until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Glivec at reduced dose of 300 mg.

Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glivec until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Glivec at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x10^9/l and/or platelets < 50 x10^9/l, repeat step 1 and resume Glivec at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	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. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Glivec until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of Glivec to 260 mg/m^2. 3. If cytopenia persists for 2 weeks, reduce further to 200 mg/m^2. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Glivec until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 200 mg/m^2.
DFSP (at dose 800 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glivec until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Glivec at 600 mg. 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Glivec at reduced dose of 400 mg.
ANC = absolute neutrophil count [a] occurring after at least 1 month of treatment		

Special populations

Paediatric population
There is no experience in children with CML below 2 years of age and with Ph+ALL below 1 year of age (see section 5.1). There is very limited experience in children with MDS/MPD, DFSP, GIST and HES/CEL.

The safety and efficacy of imatinib in children with MDS/MPD, DFSP, GIST and HES/CEL aged less than 18 years of age have not been established in clinical trials. Currently available published data are summarised in section 5.1 but no recommendation on a posology can be made.

Hepatic insufficiency
Imatinib is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections 4.4, 4.8 and 5.2).

Liver dysfunction 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

Renal insufficiency
Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. 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 sections 4.4 and 5.2).

Older people
Imatinib pharmacokinetics have not been specifically studied in older people. No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in older people.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When Glivec is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking Glivec with protease inhibitors, azole antifungals, certain macrolides (see section 4.5), CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives (see section 4.5).

Concomitant use of imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to Glivec, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Glivec (see section 4.5). Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Hepatotoxicity

Metabolism of Glivec is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2, 4.8 and 5.2). It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib 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 imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.5 and 4.8).

Fluid retention

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

Patients with cardiac disease

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

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. As cardiac adverse events have been reported uncommonly with imatinib, a careful assessment of the benefit/risk of imatinib therapy should be considered in the HES/CEL population before treatment initiation.

Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements could be associated with high eosinophil levels. Evaluation by a cardiology specialist, performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD associated with high eosinophil levels before imatinib is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1–2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported (see section 4.8). Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of Glivec treatment may be considered.

Tumour lysis syndrome

Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Glivec (see section 4.8).

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with Glivec. 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 HBV infection during treatment. Carriers of HBV who require treatment with Glivec should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Phototoxicity

Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

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). 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.

Laboratory tests

Complete blood counts must be performed regularly during therapy with Glivec. Treatment of CML patients with Glivec has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is likely to be related to 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, as recommended in section 4.2.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Glivec.

In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see section 4.2 and 5.2).

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 prescribed in accordance with standard treatment guidelines.

Paediatric population

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. In an observational study in the CML paediatric population, a statistically significant decrease (but of uncertain clinical relevance) in median height standard deviation scores after 12 and

24 months of treatment was reported in two small subsets irrespective of pubertal status or gender. Similar results have been observed in an observational study in the ALL paediatric population. Close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may **increase** imatinib plasma concentrations

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) 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.

Active substances that may **decrease** imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to Glivec, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of Glivec resulted in decrease in C_{max} and $AUC_{(0-\infty)}$ by at least 54% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with Glivec while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine and phenytoin. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.

Active substances 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 imatinib. Therefore, caution is recommended when administering Glivec with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). Glivec may increase plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

Because of known increased risks of bleeding in conjunction with the use of imatinib (e.g. haemorrhage), patients who require anticoagulation should receive low-molecular-weight or standard heparin, instead of coumarin derivatives such as warfarin.

In vitro Glivec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had an inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23% (90%CI [1.16-1.30]). Dose adjustments do not seem to be necessary when imatinib is co-administrated with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.

In vitro, Glivec inhibits paracetamol O-glucuronidation with Ki value of 58.5 micromol/l. This inhibition has not been observed *in vivo* after the administration of Glivec 400 mg and paracetamol 1000 mg. Higher doses of Glivec and paracetamol have not been studied.

Caution should therefore be exercised when using high doses of Glivec and paracetamol

concomitantly.

In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when Glivec is co-administered (see section 4.4). Caution is therefore recommended. However, the mechanism of the observed interaction is presently unknown.

In Ph+ ALL patients, there is clinical experience of co-administering Glivec with chemotherapy (see section 5.1), but drug-drug interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity (see section 4.8). Therefore, the use of Glivec in combination requires special precaution.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during treatment and for at least 15 days after stopping treatment with Glivec.

Pregnancy

There are limited data on the use of imatinib in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Glivec. Studies in animals have however shown reproductive toxicity (see section 5.3) and the potential risk for the foetus is unknown. Glivec should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

There is limited information on imatinib distribution on human milk. Studies in two breast-feeding women revealed that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient 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 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 should not breast-feed during treatment and for at least 15 days after stopping treatment with Glivec.

Fertility

In non-clinical studies, the fertility of male and female rats was not affected, although effects on reproductive parameters were observed (see section 5.3). Studies on patients receiving Glivec and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on Glivec treatment should consult with their physician.

4.7 Effects on ability to drive and use machines

Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

4.8 Undesirable effects

Patients with advanced stages of malignancies may have numerous confounding medical conditions that make causality of adverse reactions difficult to assess due to the variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medicinal products.

In clinical trials in CML, drug discontinuation for drug-related adverse reactions was observed in 2.4% of newly diagnosed patients, 4% of patients in late chronic phase after failure of interferon therapy, 4% of patients in accelerated phase after failure of interferon therapy and 5% of blast crisis patients after failure of interferon therapy. In GIST the study drug was discontinued for drug-related adverse reactions in 4% of patients.

The adverse reactions were similar in all indications, with two exceptions. There was more myelosuppression seen in CML patients than in GIST, which is probably due to the underlying disease. In the study in patients with unresectable and/or metastatic GIST, 7 (5%) patients experienced CTC grade 3/4 GI bleeds (3 patients), intra-tumoural bleeds (3 patients) or both (1 patient). GI tumour sites may have been the source of the GI bleeds (see section 4.4). GI and tumoural bleeding may be serious and sometimes fatal. The most commonly reported (≥ 10%) drug-related adverse reactions in both settings were mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of Glivec.

When imatinib was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed. Considering the limited safety database, the adverse events thus far reported in children are consistent with the known safety profile in adult patients with Ph+ ALL. The safety database for children with Ph+ALL is very limited though no new safety concerns have been identified.

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as “fluid retention”. These reactions can usually be managed by withholding Glivec temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. There were no special safety findings in paediatric clinical trials.

Adverse reactions

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.

Adverse reactions and their frequencies are reported in Table 1.

Table 1 Tabulated summary of adverse reactions

Infections and infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Not known:	Hepatitis B reactivation*
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour lysis syndrome
Not known:	Tumour haemorrhage/tumour necrosis*
Immune system disorders	
Not known:	Anaphylactic shock*

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, thrombotic microangiopathy
Metabolism and nutrition disorders	
Common:	Anorexia
Uncommon:	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare:	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
Common:	Insomnia
Uncommon:	Depression, libido decreased, anxiety
Rare:	Confusional state
Nervous system disorders	
Very common:	Headache[2]
Common:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia
Uncommon:	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage
Rare:	Increased intracranial pressure, convulsions, optic neuritis
Not known:	Cerebral oedema*
Eye disorders	
Common:	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon:	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
Rare:	Cataract, glaucoma, papilloedema
Not known:	Vitreous haemorrhage*
Ear and labyrinth disorders	
Uncommon:	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon:	Palpitations, tachycardia, cardiac failure congestive[3], pulmonary oedema
Rare:	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Not known:	Pericarditis*, cardiac tamponade*
Vascular disorders[4]	
Common:	Flushing, haemorrhage
Uncommon:	Hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Not known:	Thrombosis/embolism*
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Not known:	Acute respiratory failure[11]*, interstitial lung disease*

Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Not known:	Ileus/intestinal obstruction*, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (GAVE)*
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[8], hepatic necrosis
Skin and subcutaneous tissue disorders	
Very common:	Periorbital oedema, dermatitis/eczema/rash
Common:	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions, panniculitis[12]
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP), pemphigus*
Not known:	Palmoplantar erythrodysesthesia syndrome*, lichenoid keratosis*, lichen planus*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS)*, pseudoporphyria*
Musculoskeletal and connective tissue disorders	
Very common:	Muscle spasm and cramps, musculoskeletal pain including myalgia[9], arthralgia, bone pain[10]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness, osteonecrosis*
Rare:	Muscular weakness, arthritis, rhabdomyolysis/myopathy
Not known:	Growth retardation in children*
Renal and urinary disorders	
Uncommon:	Renal pain, haematuria, renal failure acute, urinary frequency increased
Not known:	Renal failure chronic
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
Rare:	Haemorrhagic corpus luteum/haemorrhagic ovarian cyst
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased
Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

* These types of reactions have been reported mainly from post-marketing experience with Glivec. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory

studies in unapproved indications. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to imatinib exposure.

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

2 Headache was the most common in GIST patients.

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

4 Flushing was most common in GIST patients and bleeding (haematoma, haemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).

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

6+7 Abdominal pain and gastrointestinal haemorrhage were most commonly observed in GIST patients.

8 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

9 Musculoskeletal pain during treatment with imatinib or after discontinuation has been observed in post-marketing.

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

11 Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions.

12 Including erythema nodosum.

Laboratory test abnormalities

Haematology

In 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, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 10^9/l) and thrombocytopenias (platelet count < 50 x 10^9/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59–64% and 44–63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). In newly diagnosed chronic phase CML grade 4 neutropenia (ANC < 0.5 x 10^9/l) and thrombocytopenia (platelet count < 10 x 10^9/l) were observed in 3.6% and < 1% of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a 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 the study in patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was reported in 5.4% and 0.7% of patients, respectively, and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia was seen in 7.5% and 2.7% of patients, respectively, and grade 3 thrombocytopenia in 0.7% of patients. No patient developed grade 4 thrombocytopenia. The decreases in white blood cell (WBC) and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

Biochemistry

Severe elevation of transaminases (<5%) or bilirubin (<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4.8% of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%.

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal, including one patient on high dose paracetamol.

Description of selected adverse reactions

Hepatitis B reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system. listed in Appendix V.

4.9 Overdose

Experience with doses higher than the recommended therapeutic dose is limited. Isolated cases of Glivec overdose have been reported spontaneously and in the literature. In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was “improved” or “recovered”. Events that have been reported at different dose ranges are as follows:

Adult population

1200 to 1600 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.
1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.
6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Paediatric population

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 experienced decreased white blood cell count and diarrhoea.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors, ATC code: L01EA01

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 c-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.

Pharmacodynamic effects

Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the *in vitro*, cellular and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.

In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating *kit* mutation. Constitutive activation of the PDGF receptor or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.

Clinical studies in chronic myeloid leukaemia

The effectiveness of Glivec is based on overall haematological and cytogenetic response rates and progression-free survival. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

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

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

Chronic phase, newly diagnosed
This phase III study in adult patients compared treatment with either single-agent Glivec or a combination of interferon-alpha (IFN) plus cytarabine (Ara-C). Patients showing lack of response (lack of complete haematological response (CHR) at 6 months, increasing 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 cross over to the alternative treatment arm. In the Glivec arm, patients were treated with 400 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m^2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m^2/day for 10 days/month.

A total of 1,106 patients were randomised, 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. Seven years after the last patient had been recruited, the median duration of first-line treatment was 82 and 8 months in the Glivec and IFN arms, respectively. The median duration of second-line treatment

with Glivec was 64 months. Overall, in patients receiving first-line Glivec, the average daily dose delivered was 406 ± 76 mg. The primary efficacy endpoint of the study is progression-free survival. Progression was defined as any of the following events: progression to accelerated phase or blast crisis, 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 2.

Table 2 Response in newly diagnosed CML Study (84-month data)

(Best response rates)	**Glivec** n=553	**IFN+Ara-C** n=553
Haematological response		
CHR rate n (%)	534 (96.6%)*	313 (56.6%)*
[95% CI]	[94.7%, 97.9%]	[52.4%, 60.8%]
Cytogenetic response		
Major response n (%)	490 (88.6%)*	129 (23.3%)*
[95% CI]	[85.7%, 91.1%]	[19.9%, 27.1%]
Complete CyR n (%)	456 (82.5%)*	64 (11.6%)*
Partial CyR n (%)	34 (6.1%)	65 (11.8%)
Molecular response**		
Major response at 12 months (%)	153/305=50.2%	8/83=9.6%
Major response at 24 months (%)	73/104=70.2%	3/12=25%
Major response at 84 months (%)	102/116=87.9%	3/4=75%

* p<0.001, Fischer's exact test
** molecular response percentages are based on available samples
Haematological response criteria (all responses to be confirmed after ≥ 4 weeks):
WBC < 10 x 10^9/l, platelet < 450 x 10^9/l, myelocyte+metamyelocyte < 5% in blood, no blasts and promyelocytes in blood, basophils < 20%, no extramedullary involvement
Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1–35%), minor (36–65%) or minimal (66–95%). A major response (0–35%) combines both complete and partial responses.
Major molecular response criteria: in the peripheral blood reduction of ≥ 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 improved from 12 months of therapy to 84 months of therapy as follows: CHR from 96.4% to 98.4% and CCyR from 69.5% to 87.2%, respectively.

With 7 years follow-up, there were 93 (16.8%) progression events in the Glivec arm: 37 (6.7%) involving progression to accelerated phase/blast crisis, 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 patients free of progression to accelerated phase or blast crisis at 84 months was significantly higher in the Glivec arm compared to the IFN arm (92.5% versus 85.1%, p<0.001). The annual rate of progression to accelerated phase or blast crisis decreased with time on therapy and was less than 1% annually in the fourth and fifth years. The estimated rate of progression-free survival at 84 months was 81.2% in the Glivec arm and 60.6% in the control arm (p<0.001). The yearly rates of progression of any type for Glivec also decreased over time.

A total of 71 (12.8%) and 85 (15.4%) patients died in the Glivec and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80, 87) in the randomised

Glivec and the IFN+Ara-C groups, respectively (p=0.073, log-rank test). This time-to-event endpoint is strongly affected by the high crossover rate from IFN+Ara-C to Glivec. The effect of Glivec treatment on survival in chronic phase, newly diagnosed CML has been further examined in a retrospective analysis of the above reported Glivec data with the primary data from another Phase III study using IFN+Ara-C (n=325) in an identical regimen. In this retrospective analysis, the superiority of Glivec over IFN+Ara-C in overall survival was demonstrated (p<0.001); within 42 months, 47 (8.5%) Glivec patients and 63 (19.4%) IFN+Ara-C patients had died.

The degree of cytogenetic response and molecular response had a clear effect on long-term outcomes in patients on Glivec. Whereas an estimated 96% (93%) of patients with CCyR (PCyR) at 12 months were free of progression to accelerated phase/blast crisis 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). For patients with reduction in Bcr-Abl transcripts of at least 3 logarithms at 12 months, the probability of remaining free from progression to accelerated phase/blast crisis was 99% at 84 months. Similar findings were found based on a 18-months landmark analysis.

In this study, dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. After 42 months of follow-up, 11 patients experienced a confirmed loss (within 4 weeks) of their cytogenetic response. Of these 11 patients, 4 patients escalated up to 800 mg daily, 2 of whom regained a cytogenetic response (1 partial and 1 complete, the latter also achieving a molecular response), while of the 7 patients who did not escalate the dose, only one regained a complete cytogenetic response. The percentage of some adverse reactions was higher in the 40 patients in whom the dose was increased to 800 mg daily compared to the population of patients before dose increase (n=551). The more frequent adverse reactions included gastrointestinal haemorrhages, conjunctivitis and elevation of transaminases or bilirubin. Other adverse reactions were reported with lower or equal frequency.

Chronic phase, Interferon failure
532 adult patients were treated at a starting dose of 400 mg. The patients were distributed in three main categories: haematological failure (29%), cytogenetic failure (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥ 25 x 10^6 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. The primary efficacy variable of the study was the rate of major cytogenetic response (complete plus partial response, 0 to 35% Ph+ metaphases in the bone marrow).

In this study 65% of the patients achieved a major cytogenetic response that was complete in 53% (confirmed 43%) of patients (Table 3). A complete haematological response was achieved in 95% of patients.

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

The primary efficacy variable was the rate of 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. A confirmed haematological response was achieved in 71.5% of patients (Table 3). Importantly, 27.7% of patients also achieved a major cytogenetic response, which was complete in 20.4% (confirmed 16%) of patients. For the patients treated at 600 mg, the current estimates for median progression-free-survival and overall survival were 22.9 and 42.5 months, respectively.

Myeloid blast crisis
260 patients with myeloid blast crisis were enrolled. 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg, the protocol was subsequently

amended to allow higher dosing and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the rate of 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. In this study, 31% of patients achieved a haematological response (36% in previously untreated patients and 22% in previously treated patients). The rate of response was also higher in the patients treated at 600 mg (33%) as compared to the patients treated at 400 mg (16%, p=0.0220). The current estimate of the median survival of the previously untreated and treated patients was 7.7 and 4.7 months, respectively.

Lymphoid blast crisis
A limited number of patients were enrolled in phase I studies (n=10). The rate of haematological response was 70% with a duration of 2–3 months.

Table 3 Response in adult CML studies

	Study 0110 37-month data Chronic phase, IFN failure (n=532)	Study 0109 40.5-month data Accelerated phase (n=235)	Study 0102 38-month data Myeloid blast crisis (n=260)
	% 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%
Major cytogenetic response[2]	65% (61.2–69.5)	28% (22.0–33.9)	15% (11.2–20.4)
Complete	53%	20%	7%
(Confirmed[3]) [95% CI]	(43%) [38.6–47.2]	(16%) [11.3–21.0]	(2%) [0.6–4.4]
Partial	12%	7%	8%

[1] Haematological response criteria (all responses to be confirmed after ≥ 4 weeks):
CHR: Study 0110 [WBC < 10 x 10^9/l, platelets < 450 x 10^9/l, myelocyte+metamyelocyte < 5% in blood, no blasts and promyelocytes in blood, basophils < 20%, no extramedullary involvement] and in studies 0102 and 0109 [ANC ≥ 1.5 x 10^9/l, platelets ≥ 100 x 10^9/l, no blood blasts, BM blasts < 5% and no extramedullary disease]
NEL Same criteria as for CHR but ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l (0102 and 0109 only)
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 (only for 0102 and 0109).
BM = bone marrow, PB = peripheral blood
[2] Cytogenetic response criteria:
A major response combines both complete and partial responses: complete (0% Ph+ metaphases), partial (1–35%)
[3] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

Paediatric population
A total of 26 paediatric patients of age < 18 years with either chronic phase CML (n=11) or CML in blast crisis or Ph+ acute leukaemias (n=15) were enrolled in a dose-escalation phase I trial. This was a population of heavily pretreated patients, as 46% had received prior BMT and 73% a prior multi-agent chemotherapy. Patients were treated at doses of Glivec of 260 mg/m^2/day (n=5), 340 mg/m^2/day (n=9), 440 mg/m^2/day (n=7) and 570 mg/m^2/day (n=5). Out of 9 patients with chronic phase CML and cytogenetic data available, 4 (44%) and 3 (33%) achieved a complete and partial cytogenetic response, respectively, for a rate of MCyR of 77%.

A total of 51 paediatric patients with newly diagnosed and untreated CML in chronic phase have been

enrolled in an open-label, multicentre, single-arm phase II trial. Patients were treated with Glivec 340 mg/m^2/day, with no interruptions in the absence of dose limiting toxicity. Glivec treatment induces a rapid response in newly diagnosed paediatric CML patients with a CHR of 78% after 8 weeks of therapy. The high rate of CHR is accompanied by the development of a complete cytogenetic response (CCyR) of 65% which is comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16% for a MCyR of 81%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 5.6 months.

The European Medicines Agency has waived the obligation to submit the results of studies with Glivec in all subsets of the paediatric population in Philadelphia chromosome (bcr-abl translocation)-positive chronic myeloid leukaemia (see section 4.2 for information on paediatric use).

Clinical studies in Ph+ ALL

Newly diagnosed Ph+ ALL
In a controlled study (ADE10) of imatinib versus chemotherapy induction in 55 newly diagnosed patients aged 55 years and over, imatinib used as single agent induced a significantly higher rate of complete haematological response than chemotherapy (96.3% vs. 50%; p=0.0001). When salvage therapy with imatinib was administered in patients who did not respond or who responded poorly to chemotherapy, it resulted in 9 patients (81.8%) out of 11 achieving a complete haematological response. This clinical effect was associated with a higher reduction in bcr-abl transcripts in the imatinib-treated patients than in the chemotherapy arm after 2 weeks of therapy (p=0.02). All patients received imatinib and consolidation chemotherapy (see Table 4) after induction and the levels of bcr-abl transcripts were identical in the two arms at 8 weeks. As expected on the basis of the study design, no difference was observed in remission duration, disease-free survival or overall survival, although patients with complete molecular response and remaining in minimal residual disease had a better outcome in terms of both remission duration (p=0.01) and disease-free survival (p=0.02).

The results observed in a population of 211 newly diagnosed Ph+ ALL patients in four uncontrolled clinical studies (AAU02, ADE04, AJP01 and AUS01) are consistent with the results described above. Imatinib in combination with chemotherapy induction (see Table 4) resulted in a complete haematological response rate of 93% (147 out of 158 evaluable patients) and in a major cytogenetic response rate of 90% (19 out of 21 evaluable patients). The complete molecular response rate was 48% (49 out of 102 evaluable patients). Disease-free survival (DFS) and overall survival (OS) constantly exceeded 1 year and were superior to historical control (DFS p<0.001; OS p<0.0001) in two studies (AJP01 and AUS01).

Table 4 Chemotherapy regimen used in combination with imatinib

Study ADE10	
Prephase	DEX 10 mg/m^2 oral, days 1-5; CP 200 mg/m^2 i.v., days 3, 4, 5; MTX 12 mg intrathecal, day 1
Remission induction	DEX 10 mg/m^2 oral, days 6-7, 13-16; VCR 1 mg i.v., days 7, 14; IDA 8 mg/m^2 i.v. (0.5 h), days 7, 8, 14, 15; CP 500 mg/m^2 i.v.(1 h) day 1; Ara-C 60 mg/m^2 i.v., days 22-25, 29-32
Consolidation therapy I, III, V	MTX 500 mg/m^2 i.v. (24 h), days 1, 15; 6-MP 25 mg/m^2 oral, days 1-20
Consolidation therapy II, IV	Ara-C 75 mg/m^2 i.v. (1 h), days 1-5; VM26 60 mg/m^2 i.v. (1 h), days 1-5

Study AAU02	
Induction therapy (*de novo* Ph+ ALL)	Daunorubicin 30 mg/m^2 i.v., days 1-3, 15-16; VCR 2 mg total dose i.v., days 1, 8, 15, 22; CP 750 mg/m^2 i.v., days 1, 8; Prednisone 60 mg/m^2 oral, days 1-7, 15-21; IDA 9 mg/m^2 oral, days 1-28; MTX 15 mg intrathecal, days 1, 8, 15, 22; Ara-C 40 mg intrathecal, days 1, 8, 15, 22; Methylprednisolone 40 mg intrathecal, days 1, 8, 15, 22
Consolidation (*de novo* Ph+ ALL)	Ara-C 1,000 mg/m^2/12 h i.v.(3 h), days 1-4; Mitoxantrone 10 mg/m^2 i.v. days 3-5; MTX 15 mg intrathecal, day 1; Methylprednisolone 40 mg intrathecal, day 1
Study ADE04	
Prephase	DEX 10 mg/m^2 oral, days 1-5; CP 200 mg/m^2 i.v., days 3-5; MTX 15 mg intrathecal, day 1
Induction therapy I	DEX 10 mg/m^2 oral, days 1-5; VCR 2 mg i.v., days 6, 13, 20; Daunorubicin 45 mg/m^2 i.v., days 6-7, 13-14
Induction therapy II	CP 1 g/m^2 i.v. (1 h), days 26, 46; Ara-C 75 mg/m^2 i.v. (1 h), days 28-31, 35-38, 42-45; 6-MP 60 mg/m^2 oral, days 26-46
Consolidation therapy	DEX 10 mg/m^2 oral, days 1-5; Vindesine 3 mg/m^2 i.v., day 1; MTX 1.5 g/m^2 i.v. (24 h), day 1; Etoposide 250 mg/m^2 i.v. (1 h) days 4-5; Ara-C 2x 2 g/m^2 i.v. (3 h, q 12 h), day 5
Study AJP01	
Induction therapy	CP 1.2 g/m^2 i.v. (3 h), day 1; Daunorubicin 60 mg/m^2 i.v. (1 h), days 1-3; Vincristine 1.3 mg/m^2 i.v., days 1, 8, 15, 21; Prednisolone 60 mg/m^2/day oral
Consolidation therapy	Alternating chemotherapy course: high dose chemotherapy with MTX 1 g/m^2 i.v. (24 h), day 1, and Ara-C 2 g/m^2 i.v. (q 12 h), days 2-3, for 4 cycles
Maintenance	VCR 1.3 g/m^2 i.v., day 1; Prednisolone 60 mg/m^2 oral, days 1-5
Study AUS01	
Induction-consolidation therapy	Hyper-CVAD regimen: CP 300 mg/m^2 i.v. (3 h, q 12 h), days 1-3; Vincristine 2 mg i.v., days 4, 11; Doxorubicine 50 mg/m^2 i.v. (24 h), day 4; DEX 40 mg/day on days 1-4 and 11-14, alternated with MTX 1 g/m^2 i.v. (24 h), day 1, Ara-C 1 g/m^2 i.v. (2 h, q 12 h), days 2-3 (total of 8 courses)
Maintenance	VCR 2 mg i.v. monthly for 13 months; Prednisolone 200 mg oral, 5 days per month for 13 months
All treatment regimens include administration of steroids for CNS prophylaxis.	
Ara-C: cytosine arabinoside; CP: cyclophosphamide; DEX: dexamethasone; MTX: methotrexate; 6-MP: 6-mercaptopurine VM26: Teniposide; VCR: vincristine; IDA: idarubicine; i.v.: intravenous	

Paediatric population

In study I2301, a total of 93 paediatric, adolescent and young adult patients (from 1 to 22 years old) with Ph+ ALL were enrolled in an open-label, multicentre, sequential cohort, non-randomised phase III trial, and were treated with Glivec (340 mg/m^2/day) in combination with intensive chemotherapy after induction therapy. Glivec was administered intermittently in cohorts 1-5, with increasing duration

and earlier start of Glivec from cohort to cohort; cohort 1 receiving the lowest intensitiy and cohort 5 receiving the highest intensity of Glivec (longest duration in days with continuous daily Glivec dosing during the first chemotherapy treatment courses). Continuous daily exposure to Glivec early in the course of treatment in combination with chemotherapy in cohort 5-patients (n=50) improved the 4-year event-free survival (EFS) compared to historical controls (n=120), who received standard chemotherapy without Glivec (69.6% vs. 31.6%, respectively). The estimated 4-year OS in cohort 5-patients was 83.6% compared to 44.8% in the historical controls. 20 out of the 50 (40%) patients in cohort 5 received haematopoietic stem cell transplant.

Table 5 Chemotherapy regimen used in combination with imatinib in study I2301

Consolidation block 1 (3 weeks)	VP-16 (100 mg/m^2/day, IV): days 1-5 Ifosfamide (1.8 g/m^2/day, IV): days 1-5 MESNA (360 mg/m^2/dose q3h, x 8 doses/day, IV): days 1-5 G-CSF (5 µg/kg, SC): days 6-15 or until ANC > 1500 post nadir IT Methotrexate (age-adjusted): day 1 ONLY Triple IT therapy (age-adjusted): day 8, 15
Consolidation block 2 (3 weeks)	Methotrexate (5 g/m^2 over 24 hours, IV): day 1 Leucovorin (75 mg/m^2 at hour 36, IV; 15 mg/m^2 IV or PO q6h x 6 doses)iii: Days 2 and 3 Triple IT therapy (age-adjusted): day 1 ARA-C (3 g/m^2/dose q 12 h x 4, IV): days 2 and 3 G-CSF (5 µg/kg, SC): days 4-13 or until ANC > 1500 post nadir
Reinduction block 1 (3 weeks)	VCR (1.5 mg/m^2/day, IV): days 1, 8, and 15 DAUN (45 mg/m^2/day bolus, IV): days 1 and 2 CPM (250 mg/m^2/dose q12h x 4 doses, IV): days 3 and 4 PEG-ASP (2500 IUnits/m^2, IM): day 4 G-CSF (5 µg/kg, SC): days 5-14 or until ANC > 1500 post nadir Triple IT therapy (age-adjusted): days 1 and 15 DEX (6 mg/m^2/day, PO): days 1-7 and 15-21
Intensification block 1 (9 weeks)	Methotrexate (5 g/m^2 over 24 hours, IV): days 1 and 15 Leucovorin (75 mg/m^2 at hour 36, IV; 15 mg/m^2 IV or PO q6h x 6 doses)iii: Days 2, 3, 16, and 17 Triple IT therapy (age-adjusted): days 1 and 22 VP-16 (100 mg/m^2/day, IV): days 22-26 CPM (300 mg/m^2/day, IV): days 22-26 MESNA (150 mg/m^2/day, IV): days 22-26 G-CSF (5 µg/kg, SC): days 27-36 or until ANC > 1500 post nadir ARA-C (3 g/m^2, q12h, IV): days 43, 44 L-ASP (6000 IUnits/m^2, IM): day 44
Reinduction block 2 (3 weeks)	VCR (1.5 mg/m^2/day, IV): days 1, 8 and 15 DAUN (45 mg/m^2/day bolus, IV): days 1 and 2 CPM (250 mg/m^2/dose q12h x 4 doses, iv): Days 3 and 4 PEG-ASP (2500 IUnits/m^2, IM): day 4 G-CSF (5 µg/kg, SC): days 5-14 or until ANC > 1500 post nadir Triple IT therapy (age-adjusted): days 1 and 15 DEX (6 mg/m^2/day, PO): days 1-7 and 15-21
Intensification block 2 (9 weeks)	Methotrexate (5 g/m^2 over 24 hours, IV): days 1 and 15 Leucovorin (75 mg/m^2 at hour 36, IV; 15 mg/m^2 IV or PO q6h x 6 doses)iii: days 2, 3, 16, and 17 Triple IT therapy (age-adjusted): days 1 and 22 VP-16 (100 mg/m^2/day, IV): days 22-26 CPM (300 mg/m^2/day, IV): days 22-26 MESNA (150 mg/m^2/day, IV): days 22-26 G-CSF (5 µg/kg, SC): days 27-36 or until ANC > 1500 post nadir ARA-C (3 g/m^2, q12h, IV): days 43, 44 L-ASP (6000 IUnits/m^2, IM): day 44

Maintenance (8-week cycles) Cycles 1–4	MTX (5 g/m^2 over 24 hours, IV): day 1 Leucovorin (75 mg/m^2 at hour 36, IV; 15 mg/m^2 IV or PO q6h x 6 doses)iii: days 2 and 3 Triple IT therapy (age-adjusted): days 1, 29 VCR (1.5 mg/m^2, IV): days 1, 29 DEX (6 mg/m^2/day PO): days 1-5; 29-33 6-MP (75 mg/m^2/day, PO): days 8-28 Methotrexate (20 mg/m^2/week, PO): days 8, 15, 22 VP-16 (100 mg/m^2, IV): days 29-33 CPM (300 mg/m^2, IV): days 29-33 MESNA IV days 29-33 G-CSF (5 µg/kg, SC): days 34-43
Maintenance (8-week cycles) Cycle 5	Cranial irradiation (Block 5 only) 12 Gy in 8 fractions for all patients that are CNS1 and CNS2 at diagnosis 18 Gy in 10 fractions for patients that are CNS3 at diagnosis VCR (1.5 mg/m^2/day, IV): days 1, 29 DEX (6 mg/m^2/day, PO): days 1-5; 29-33 6-MP (75 mg/m^2/day, PO): days 11-56 (Withhold 6-MP during the 6-10 days of cranial irradiation beginning on day 1 of Cycle 5. Start 6-MP the 1st day after cranial irradiation completion.) Methotrexate (20 mg/m^2/week, PO): days 8, 15, 22, 29, 36, 43, 50
Maintenance (8-week cycles) Cycles 6-12	VCR (1.5 mg/m^2/day, IV): days 1, 29 DEX (6 mg/m^2/day, PO): days 1-5; 29-33 6-MP (75 mg/m^2/day, PO): days 1-56 Methotrexate (20 mg/m^2/week, PO): days 1, 8, 15, 22, 29, 36, 43, 50

G-CSF = granulocyte colony stimulating factor, VP-16 = etoposide, MTX = methotrexate, IV = intravenous, SC = subcutaneous, IT = intrathecal, PO = oral, IM = intramuscular, ARA-C = cytarabine, CPM = cyclophosphamide, VCR = vincristine, DEX = dexamethasone, DAUN = daunorubicin, 6-MP = 6-mercaptopurine, E.Coli L-ASP = L-asparaginase, PEG-ASP = PEG asparaginase, MESNA= 2-mercaptoethane sulfonate sodium, iii= or until MTX level is < 0.1 µM, q6h = every 6 hours, Gy= Gray

Study AIT07 was a multicentre, open-label, randomised, phase II/III study that included 128 patients (1 to < 18 years) treated with imatinib in combination with chemotherapy. Safety data from this study seem to be in line with the safety profile of imatinib in Ph+ ALL patients.

Relapsed/refractory Ph+ ALL

When imatinib was used as single agent in patients with relapsed/refractory Ph+ ALL, it resulted, in the 53 out of 411 patients evaluable for response, in a haematological response rate of 30% (9% complete) and a major cytogenetic response rate of 23%. (Of note, out of the 411 patients, 353 were treated in an expanded access program without primary response data collected.) The median time to progression in the overall population of 411 patients with relapsed/refractory Ph+ ALL ranged from 2.6 to 3.1 months, and median overall survival in the 401 evaluable patients ranged from 4.9 to 9 months. The data was similar when re-analysed to include only those patients age 55 or older.

Clinical studies in MDS/MPD

Experience with Glivec in this indication is very limited and is based on haematological and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit or increased survival. One open label, multicentre, phase II clinical trial (study B2225) was conducted testing Glivec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD who were treated with Glivec 400 mg daily. Three patients presented a complete haematological response (CHR) and one patient experienced a partial haematological response (PHR). At the time of the original analysis, three of the four patients with detected PDGFR gene rearrangements developed haematological response (2 CHR and 1 PHR). The age of these patients ranged from 20 to 72 years.

An observational registry (study L2401) was conducted to collect long-term safety and efficacy data in patients suffering from myeloproliferative neoplasms with PDGFR- β rearrangement and who were treated with Glivec. The 23 patients enrolled in this registry received Glivec at a median daily dose of 264 mg (range: 100 to 400 mg) for a median duration of 7.2 years (range 0.1 to 12.7 years). Due to the observational nature of this registry, haematologic, cytogenetic and molecular assessment data were available for 22, 9 and 17 of the 23 enrolled patients, respectively. When assuming conservatively that patients with missing data were non-responders, CHR was observed in 20/23 (87%) patients, CCyR in 9/23 (39.1%) patients, and MR in 11/23 (47.8%) patients, respectively. When the response rate is calculated from patients with at least one valid assessment, the response rate for CHR, CCyR and MR was 20/22 (90.9%), 9/9 (100%) and 11/17 (64.7%), respectively.

In addition a further 24 patients with MDS/MPD were reported in 13 publications. 21 patients were treated with Glivec 400 mg daily, while the other 3 patients received lower doses. In eleven patients PDGFR gene rearrangements was detected, 9 of them achieved a CHR and 1 PHR. The age of these patients ranged from 2 to 79 years. In a recent publication updated information from 6 of these 11 patients revealed that all these patients remained in cytogenetic remission (range 32-38 months). The same publication reported long term follow-up data from 12 MDS/MPD patients with PDGFR gene rearrangements (5 patients from study B2225). These patients received Glivec for a median of 47 months (range 24 days – 60 months). In 6 of these patients follow-up now exceeds 4 years. Eleven patients achieved rapid CHR; ten had complete resolution of cytogenetic abnormalities and a decrease or disappearance of fusion transcripts as measured by RT-PCR. Haematological and cytogenetic responses have been sustained for a median of 49 months (range 19-60) and 47 months (range 16-59), respectively. The overall survival is 65 months since diagnosis (range 25-234). Glivec administration to patients without the genetic translocation generally results in no improvement.

There are no controlled trials in paediatric patients with MDS/MPD. Five (5) patients with MDS/MPD associated with PDGFR gene re-arrangements were reported in 4 publications. The age of these patients ranged from 3 months to 4 years and imatinib was given at dose 50 mg daily or doses ranging from 92.5 to 340 mg/m^2 daily. All patients achieved complete haematological response, cytogenetic response and/or clinical response.

Clinical studies in HES/CEL

One open-label, multicentre, phase II clinical trial (study B2225) was conducted testing Glivec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. In this study, 14 patients with HES/CEL were treated with 100 mg to 1,000 mg of Glivec daily. A further 162 patients with HES/CEL, reported in 35 published case reports and case series received Glivec at doses from 75 mg to 800 mg daily. Cytogenetic abnormalities were evaluated in 117 of the total population of 176 patients. In 61 of these 117 patients FIP1L1-PDGFRα fusion kinase was identified. An additional four HES patients were found to be FIP1L1-PDGFRα-positive in other 3 published reports. All 65 FIP1L1-PDGFRα fusion kinase positive patients achieved a CHR sustained for months (range from 1+ to 44+ months censored at the time of the reporting). As reported in a recent publication 21 of these 65 patients also achieved complete molecular remission with a median follow-up of 28 months (range 13-67 months). The age of these patients ranged from 25 to 72 years. 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.

There are no controlled trials in paediatric patients with HES/CEL. Three (3) patients with HES and CEL associated with PDGFR gene re-arrangements were reported in 3 publications. The age of these patients ranged from 2 to 16 years and imatinib was given at dose 300 mg/m^2 daily or doses ranging from 200 to 400 mg daily. All patients achieved complete haematological response, complete cytogenetic response and/or complete molecular response.

Clinical studies in unresectable and/or metastatic GIST

One phase II, open-label, randomised, uncontrolled 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 orally once 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. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex method after antigen retrieval.

The primary evidence of efficacy was based on objective response rates. Tumours were required to be measurable in at least one site of disease, and response characterisation based on Southwestern Oncology Group (SWOG) criteria. Results are provided in Table 6.

Table 6 Best tumour response in trial STIB2222 (GIST)

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

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

In two clinical studies (study B2222 and an intergroup study S0033) the daily dose of Glivec was escalated to 800 mg in patients progressing at the lower daily doses of 400 mg or 600 mg. The daily dose was escalated to 800 mg in a total of 103 patients; 6 patients achieved a partial response and 21 stabilisation of their disease after dose escalation for an overall clinical benefit of 26%. From the safety data available, escalating the dose to 800 mg daily in patients progressing at lower doses of 400 mg or 600 mg daily does not seem to affect the safety profile of Glivec.

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 773 patients. The ages of these patients ranged from 18 to 91 years. Patients were included who had a histological 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 14-70 days prior to registration. After resection of primary GIST, patients were randomised 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 randomisation to the date of recurrence or death from any cause.

Glivec significantly prolonged RFS, with 75% of patients being recurrence-free at 38 months in the Glivec group vs. 20 months in the placebo group (95% CIs, [30 - non-estimable]; [14 - non-estimable],

respectively); (hazard ratio = 0.398 [0.259-0.610], p<0.0001). At one year the overall RFS was significantly better for Glivec (97.7%) vs. placebo (82.3%), (p<0.0001). The risk of recurrence was thus reduced by approximately 89% as compared with placebo (hazard ratio = 0.113 [0.049-0.264]).

The risk of recurrence in patients after surgery of their primary GIST was retrospectively assessed based on the following prognostic factors: tumour size, mitotic index, tumour location. Mitotic index data were available for 556 of the 713 intention-to-treat (ITT) population. The results of subgroup analyses according to the United States National Institutes of Health (NIH) and the Armed Forces Institute of Pathology (AFIP) risk classifications are shown in Table 7. No benefit was observed in the low and very low risk groups. No overall survival benefit has been observed.

Table 7 Summary of Z9001 trial RFS analyses by NIH and AFIP risk classifications

Risk criteria	Risk Level	% of patients	No. of events / No. of patients	Overall hazard ratio (95%CI)*	RFS rates (%)	
					12 month	24 month
			Glivec vs placebo		Glivec vs placebo	Glivec vs placebo
NIH	Low	29.5	0/86 vs. 2/90	N.E.	100 vs. 98.7	100 vs. 95.5
	Intermediate	25.7	4/75 vs. 6/78	0.59 (0.17; 2.10)	100 vs. 94.8	97.8 vs. 89.5
	High	44.8	21/140 vs. 51/127	0.29 (0.18; 0.49)	94.8 vs. 64.0	80.7 vs. 46.6
AFIP	Very Low	20.7	0/52 vs. 2/63	N.E.	100 vs. 98.1	100 vs. 93.0
	Low	25.0	2/70 vs. 0/69	N.E.	100 vs. 100	97.8 vs. 100
	Moderate	24.6	2/70 vs. 11/67	0.16 (0.03; 0.70)	97.9 vs. 90.8	97.9 vs. 73.3
	High	29.7	16/84 vs. 39/81	0.27 (0.15; 0.48)	98.7 vs. 56.1	79.9 vs. 41.5

* Full follow-up period; NE – Not estimable

A second multicentre, open label phase III study (SSG XVIII/AIO) compared 400 mg/day Glivec 12 months treatment vs. 36 months treatment in patients after surgical resection of GIST and one of the following: 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 randomised 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 randomisation to data cut-off), with a total of 83 months between the first patient randomised and the cut-off date.

The primary endpoint of the study was recurrence-free survival (RFS), defined as the time from date of randomisation 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) (Table 8, Figure 1).

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 8, Figure 2).

Longer duration of the treatment (> 36 months) may delay the onset of further recurrences; however the impact of this finding on the overall survival remains unknown.

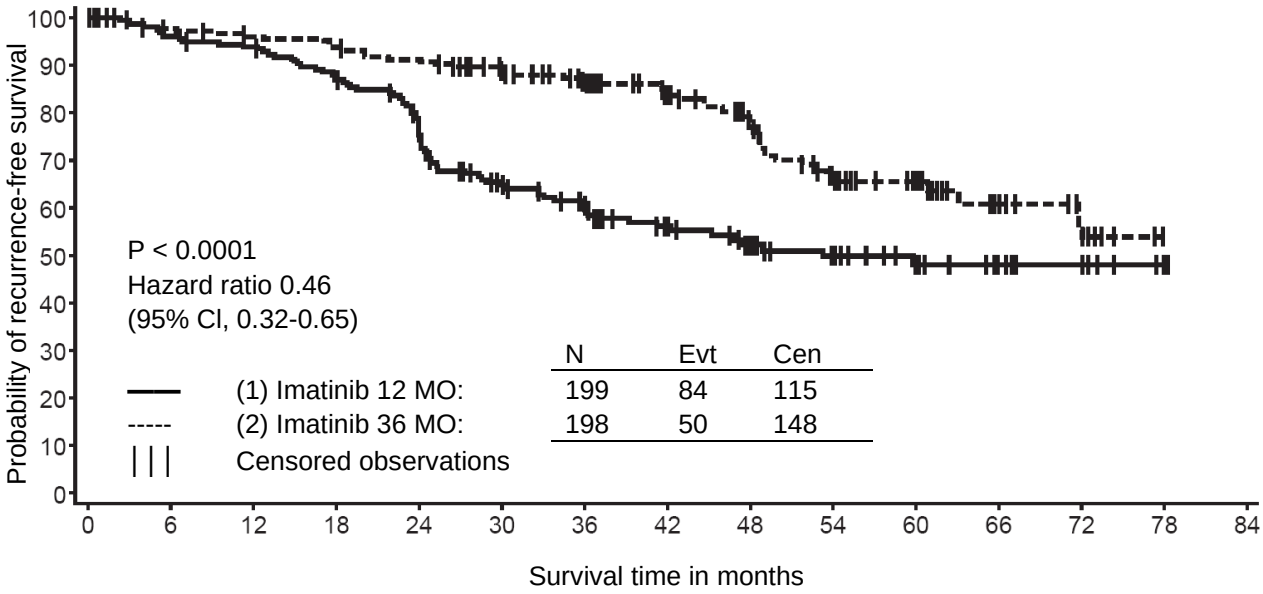
The total number of deaths were 25 for the 12-month treatment arm and 12 for the 36-month treatment arm.

Treatment with imatinib for 36 months was superior to treatment for 12 months in the ITT analysis, i.e. including the entire study population. In a planned subgroup analysis by mutation type, the HR for RFS for 36 months of treatment for patients with mutations of exon 11 was 0.35 [95% CI: 0.22, 0.56]. No conclusions can be drawn for other less common mutation subgroups due to the low number of observed events.

Table 8 12-month and 36-month Glivec treatment (SSGXVIII/AIO Trial)

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

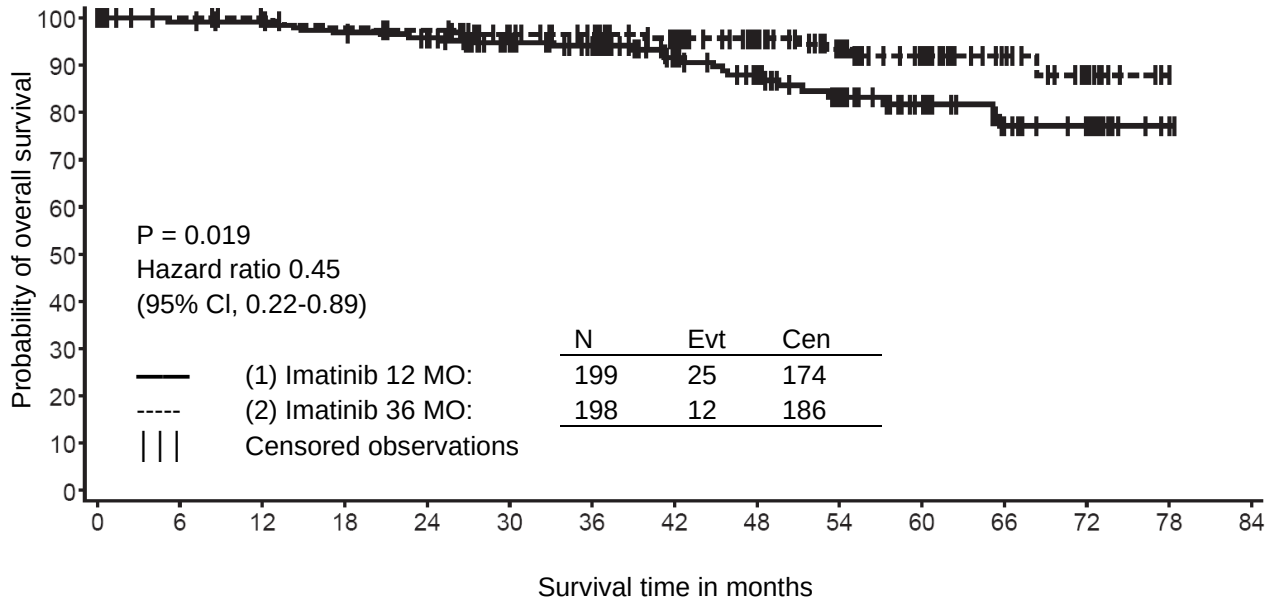
Figure 1 Kaplan-Meier estimates for primary recurrence-free survival endpoint (ITT population)



At-risk : Events

(1)	199:0	182:8	177:12	163:25	137:46	105:65	88:72	61:77	49:81	36:83	27:84	14:84	10:84	2:84	0:84
(2)	198:0	189:5	184:8	181:11	173:18	152:22	133:25	102:29	82:35	54:46	39:47	21:49	8:50	0:50	

Figure 2 Kaplan-Meier estimates for overall survival (ITT population)



At-risk : Events

(1)	199:0	190:2	188:2	183:6	176:8	156:10	140:11	105:14	87:18	64:22	46:23	27:25	20:25	2:25	0:25
(2)	198:0	196:0	192:0	187:4	184:5	164:7	152:7	119:8	100:8	76:10	56:11	31:11	13:12	0:12	

There are no controlled trials in paediatric patients with c-Kit positive GIST. Seventeen (17) patients with GIST (with or without Kit and PDGFR mutations) were reported in 7 publications. The age of these patients ranged from 8 to 18 years and imatinib was given in both adjuvant and metastatic settings at doses ranging from 300 to 800 mg daily. The majority of paediatric patients treated for GIST lacked data confirming c-kit or PDGFR mutations which may have led to mixed clinical outcomes.

Clinical studies in DFSP

One phase II, open label, multicentre clinical trial (study B2225) was conducted including 12 patients with DFSP 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. The primary evidence of efficacy was based on objective response rates. Out of the 12 patients enrolled, 9 responded, one completely and 8 partially. Three of the partial responders were subsequently rendered disease free by surgery. The median duration of therapy in study B2225 was 6.2 months, with a maximum duration of 24.3 months. 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 adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Glivec daily. Five (5) patients responded, 3 completely and 2 partially. The median duration of therapy in the published literature ranged between 4 weeks and more than 20 months. The translocation t(17:22)[(q22:q13)], or its gene product, was present in nearly all responders to Glivec treatment.

There are no controlled trials in paediatric patients with DFSP. Five (5) patients with DFSP and PDGFR gene re-arrangements were reported in 3 publications. The age of these patients ranged from newborn to 14 years and imatinib was given at dose 50 mg daily or doses ranging from 400 to 520 mg/m^2 daily. All patients achieved partial and/or complete response.

5.2 Pharmacokinetic properties

Pharmacokinetics of Glivec

The pharmacokinetics of Glivec have been evaluated over a dosage range of 25 to 1,000 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

Mean absolute bioavailability for imatinib is 98%. There was high between-patient variability in plasma imatinib AUC levels after an oral dose. When given with a high-fat meal, the rate of absorption of imatinib was minimally reduced (11% decrease in C_{max} and prolongation of t_{max} by 1.5 h), with a small reduction in AUC (7.4%) compared to fasting conditions. The effect of prior gastrointestinal surgery on drug absorption has not been investigated.

Distribution

At clinically relevant concentrations of imatinib, binding to plasma proteins was approximately 95% on the basis of *in vitro* experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

Biotransformation

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

Imatinib and the N-demethyl metabolite together accounted for about 65% of the circulating radioactivity ($AUC_{(0\text{-}48h)}$). The remaining circulating radioactivity consisted of a number of minor metabolites.

The *in vitro* results showed that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin (IC_{50} 50 µM) and fluconazole (IC_{50} 118 µM) showed inhibition of imatinib metabolism which could have clinical relevance.

Imatinib was shown *in vitro* to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5. K_i values in human liver microsomes were 27, 7.5 and 7.9 µmol/l, respectively. Maximal plasma concentrations of imatinib in patients are 2–4 µmol/l, consequently an inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil, but it inhibited paclitaxel metabolism as a result of competitive inhibition of CYP2C8 (K_i = 34.7 µM). This K_i value is far higher than the expected plasma levels of imatinib in patients, consequently no interaction is expected upon co-administration of either 5-fluorouracil or paclitaxel and imatinib.

Elimination

Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of imatinib, approximately 81% of the dose was recovered 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.

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the $t_{½}$ was approximately 18 h, suggesting that

once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25–1,000 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.

Pharmacokinetics in GIST patients

In patients with GIST steady-state exposure was 1.5-fold higher than that observed for CML patients for the same dosage (400 mg daily). Based on preliminary population pharmacokinetic analysis in GIST patients, there were three variables (albumin, WBC and bilirubin) found to have a statistically significant relationship with imatinib pharmacokinetics. Decreased values of albumin caused a reduced clearance (CL/f); and higher levels of WBC led to a reduction of CL/f. However, these associations are not sufficiently pronounced to warrant dose adjustment. In this patient population, the presence of hepatic metastases could potentially lead to hepatic insufficiency and reduced metabolism.

Population pharmacokinetics

Based on population pharmacokinetic analysis in CML patients, there was a small effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant. The effect of bodyweight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 l/h, while for a patient weighing 100 kg the clearance will rise to 11.8 l/h. These changes are not considered sufficient to warrant dose adjustment based on kg bodyweight. There is no effect of gender on the kinetics of imatinib.

Pharmacokinetics in children

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m^2/day achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on day 8 and day 1 at the 340 mg/m^2/day dose level revealed a 1.7-fold drug accumulation after repeated once-daily dosing.

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/m^2 once daily (not exceeding 400 mg once daily) or 340 mg/m^2 once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

Organ function impairment

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5- to 2-fold, corresponding to a 1.5-fold elevation of plasma AGP, to which imatinib binds strongly. The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib (see sections 4.2 and 4.4).

Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function (see sections 4.2, 4.4 and 4.8).

5.3 Preclinical safety data

The preclinical safety profile of imatinib was assessed in rats, dogs, monkeys and rabbits.

Multiple dose toxicity studies revealed mild to moderate haematological changes in rats, dogs and monkeys, accompanied by bone marrow changes in rats and dogs.

The liver was a target organ in rats and dogs. Mild to moderate increases in transaminases and slight decreases in cholesterol, triglycerides, total protein and albumin levels were observed in both species. No histopathological changes were seen in rat liver. Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia.

Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralisation and dilation of the renal tubules and tubular nephrosis. Increased blood urea nitrogen (BUN) and creatinine were observed in several of these animals. In rats, hyperplasia of the transitional epithelium in the renal papilla and in the urinary bladder was observed at doses ≥ 6 mg/kg in the 13-week study, without changes in serum or urinary parameters. An increased rate of opportunistic infections was observed with chronic imatinib treatment.

In a 39-week monkey study, no NOAEL (no observed adverse effect level) was established at the lowest dose of 15 mg/kg, approximately one-third the maximum human dose of 800 mg based on body surface. Treatment resulted in worsening of normally suppressed malarial infections in these animals.

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

In a study of fertility, in male rats dosed for 70 days prior to mating, 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 ≤ 20 mg/kg. A slight to moderate reduction in spermatogenesis was also observed in the dog at oral doses ≥ 30 mg/kg. When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females. At a dose of 60 mg/kg, female rats had significant post-implantation foetal loss and a reduced number of live foetuses. This was not seen at doses ≤ 20 mg/kg.

In an oral pre- and postnatal development study in rats, red vaginal discharge was noted in the 45 mg/kg/day group on either day 14 or day 15 of gestation. At the same dose, the number of stillborn pups as well as those dying between postpartum days 0 and 4 was increased. In the F_1 offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. F_1 fertility was not affected, while an increased number of resorptions and a decreased number of viable foetuses was noted at 45 mg/kg/day. The no observed effect level (NOEL) for both the maternal animals and the F_1 generation was 15 mg/kg/day (one quarter of the maximum human dose of 800 mg).

Imatinib was teratogenic in rats when administered during organogenesis at doses ≥ 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. These effects were not seen at doses ≤ 30 mg/kg.

No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 postpartum) with respect to the known target organs in adult rats. In the juvenile toxicology study, effects upon growth, delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m^2. In addition, mortality was observed in juvenile animals (around weaning phase) at

approximately 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m^2.

In the 2-year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach.

Papilloma/carcinoma of the preputial/clitoral gland were noted from 30 mg/kg/day onwards, representing approximately 0.5 or 0.3 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 times the daily exposure in children (based on AUC) at 340 mg/m^2/day. The no observed effect level (NOEL) was 15 mg/kg/day. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day, representing approximately 1.7 or 1 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 1.2 times the daily exposure in children (based on AUC) at 340 mg/m^2/day. The no observed effect level (NOEL) was 30 mg/kg/day.

The mechanism and relevance of these findings in the rat carcinogenicity study for humans are not yet clarified.

Non-neoplastic lesions not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

The active substance imatinib demonstrates an environmental risk for sediment organisms.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Tablet coat:
Iron oxide, red (E172)
Iron oxide, yellow (E172)
Macrogol
Talc
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Glivec 100 mg film-coated tablets

Do not store above 30°C.

Glivec 400 mg film-coated tablets

Store below 25°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Glivec 100 mg film-coated tablets

PVC/alu blisters
Packs containing 20, 60, 120 or 180 film-coated tablets

PVDC/alu blisters
Packs containing 60, 120 or 180 film-coated tablets

Glivec 400 mg film-coated tablets

PVDC/alu blisters
Packs containing 10, 30 or 90 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Glivec 100 mg film-coated tablets

EU/1/01/198/007
EU/1/01/198/008
EU/1/01/198/011
EU/1/01/198/012
EU/1/01/198/014
EU/1/01/198/015
EU/1/01/198/016

Glivec 400 mg film-coated tablets

EU/1/01/198/009
EU/1/01/198/010
EU/1/01/198/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 November 2001
Date of latest renewal: 07 November 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana, 1000
Slovenia

Lek d.d, PE PROIZVODNJA LENDAVA
Trimlini 2D
Lendava, 9220
Slovenia

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Glivec 100 mg film-coated tablets
imatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg imatinib (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
60 film-coated tablets
120 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/198/007	20 tablets (PVC/alu blisters)
EU/1/01/198/008	60 tablets (PVC/alu blisters)
EU/1/01/198/011	120 tablets (PVC/alu blisters)
EU/1/01/198/012	180 tablets (PVC/alu blisters)
EU/1/01/198/014	60 tablets (PVDC/alu blisters)
EU/1/01/198/015	120 tablets (PVDC/alu blisters)
EU/1/01/198/016	180 tablets (PVDC/alu blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Glivec 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Glivec 100 mg tablets
imatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Glivec 400 mg film-coated tablets
imatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg of imatinib (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/198/009	10 tablets
EU/1/01/198/010	30 tablets
EU/1/01/198/013	90 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Glivec 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Glivec 400 mg tablets
imatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Glivec 100 mg film-coated tablets
Glivec 400 mg film-coated tablets
imatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Glivec is and what it is used for
2. What you need to know before you take Glivec
3. How to take Glivec
4. Possible side effects
5. How to store Glivec
6. Contents of the pack and other information

1. What Glivec is and what it is used for

Glivec is a medicine containing an active substance called imatinib. This medicine works by inhibiting the growth of abnormal cells in the diseases listed below. These include some types of cancer.

Glivec is a treatment for adults and children for:

- **Chronic myeloid leukaemia (CML).** Leukaemia is a cancer of white blood cells. These white cells usually help the body to fight infection. Chronic myeloid leukaemia is a form of leukaemia in which certain abnormal white cells (named myeloid cells) start growing out of control.
- **Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph-positive ALL)**. Leukaemia is a cancer of white blood cells. These white cells usually help the body to fight infection. Acute lymphoblastic leukaemia is a form of leukaemia in which certain abnormal white cells (named lymphoblasts) start growing out of control. Glivec inhibits the growth of these cells.

Glivec is also a treatment for adults for:

- **Myelodysplastic/myeloproliferative diseases (MDS/MPD).** These are a group of blood diseases in which some blood cells start growing out of control. Glivec inhibits the growth of these cells in a certain subtype of these diseases.
- **Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).** These are blood diseases in which some blood cells (named eosinophils) start growing out of control. Glivec inhibits the growth of these cells in a certain subtype of these diseases.
- **Gastrointestinal stromal tumours (GIST).** GIST is a cancer of the stomach and bowels. It arises from uncontrolled cell growth of the supporting tissues of these organs.
- **Dermatofibrosarcoma protuberans (DFSP).** DFSP is a cancer of the tissue beneath the skin in which some cells start growing out of control. Glivec inhibits the growth of these cells.

In the rest of this leaflet, we will use the abbreviations when talking about these diseases.

If you have any questions about how Glivec works or why this medicine has been prescribed for you,

ask your doctor.

2. What you need to know before you take Glivec

Glivec will only be prescribed to you by a doctor with experience in medicines to treat blood cancers or solid tumours.

Follow all your doctor's instructions carefully, even if they differ from the general information contained in this leaflet.

Do not take Glivec
- if you are allergic to imatinib or any of the other ingredients of this medicine (listed in section 6).

If this applies to you, **tell your doctor without taking Glivec.**

If you think you may be allergic but are not sure, ask your doctor for advice.

Warnings and precautions
Talk to your doctor before taking Glivec:
- if you have or have ever had a liver, kidney or heart problem.
- if you are taking the medicine levothyroxine because your thyroid has been removed.
- if you have ever had or might now have a hepatitis B infection. This is because Glivec could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you experience bruising, bleeding, fever, fatigue and confusion when taking Glivec, contact your doctor. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA).

If any of these apply to you, **tell your doctor before taking Glivec.**

You may become more sensitive to the sun while taking Glivec. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF). These precautions are also applicable to children.

During treatment with Glivec, tell your doctor straight away if you put on weight very quickly. Glivec may cause your body to retain water (severe fluid retention).

While you are taking Glivec, your doctor will regularly check whether the medicine is working. You will also have blood tests and be weighed regularly.

Children and adolescents
Glivec is also a treatment for children with CML. There is no experience in children with CML below 2 years of age. There is limited experience in children with Ph-positive ALL and very limited experience in children with MDS/MPD, DFSP, GIST and HES/CEL.

Some children and adolescents taking Glivec may have slower than normal growth. The doctor will monitor the growth at regular visits.

Other medicines and Glivec
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (such as paracetamol) and including herbal medicines (such as St. John's Wort). Some medicines can interfere with the effect of Glivec when taken together. They may increase or decrease the effect of Glivec, either leading to increased side effects or making Glivec less effective. Glivec may do the same to some other medicines.

Tell your doctor if you are using medicines that prevent the formation of blood clots.

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- Glivec is not recommended during pregnancy unless clearly necessary as it may harm your baby. Your doctor will discuss with you the possible risks of taking Glivec during pregnancy.
- Women who might become pregnant are advised to use effective contraception during treatment and for 15 days after ending treatment.
- Do not breast-feed during the treatment with Glivec and for 15 days after ending treatment, as it may harm your baby.
- Patients who are concerned about their fertility while taking Glivec are advised to consult with their doctor.

Driving and using machines

You may feel dizzy or drowsy or get blurred vision while taking this medicine. If this happens, do not drive or use any tools or machines until you are feeling well again.

3. How to take Glivec

Your doctor has prescribed Glivec because you suffer from a serious condition. Glivec can help you to fight this condition.

However, always take this medicine exactly as your doctor or pharmacist has told you. It is important that you do this as long as your doctor or pharmacist tells you to. Check with your doctor or pharmacist if you are not sure.

Do not stop taking Glivec unless your doctor tells you to. If you are not able to take the medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor straight away.

How much Glivec to take

Use in adults

Your doctor will tell you exactly how many tablets of Glivec to take.

- **If you are being treated for CML:**
  Depending on your condition the usual starting dose is either **400 mg** or **600 mg** to be taken **once** a day.

- **If you are being treated for GIST:**
  The starting dose is 400 mg, to be taken **once** a day.

For CML and GIST, your doctor may prescribe a higher or lower dose depending on how you respond to the treatment. If your daily dose is 800 mg, you should take 400 mg in the morning and 400 mg in the evening.

- **If you are being treated for Ph-positive ALL:**
  The starting dose is 600 mg to be taken **once** a day.

- **If you are being treated for MDS/MPD:**
  The starting dose is 400 mg to be taken **once** a day.

- **If you are being treated for HES/CEL:**
  The starting dose is 100 mg, to be taken **once** a day. Your doctor may decide to increase the dose to 400 mg, to be taken **once** a day, depending on how you respond to treatment.

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

A 400 mg dose can be taken either as 1 tablet of 400 mg or 4 tablets of 100 mg.
A 600 mg dose can be taken either as 1 tablet of 400 mg plus 2 tablets of 100 mg or as 1 tablet of 400 mg plus half of 1 tablet of 400 mg.

The tablets can be divided in half by breaking along the score line.

Use in children and adolescents
The doctor will tell you how many tablets of Glivec to give to your child. The amount of Glivec given will depend on your child's condition, body weight and height. The total daily dose in children must not exceed 800 mg with CML and 600 mg with Ph+ALL. The treatment can either be given to your child as a once-daily dose or alternatively the daily dose can be split into two administrations (half in the morning and half in the evening).

When and how to take Glivec
- **Take Glivec with a meal.** This will help protect you from stomach problems when taking Glivec.
- **Swallow the tablets whole with a large glass of water.**

If you are unable to swallow the tablets, you can dissolve them in a glass of still water or apple juice:
- Use about 50 ml for each 100 mg tablet or 200 ml for each 400 mg tablet.
- Stir with a spoon until the tablets have completely dissolved.
- Once the tablet has dissolved, drink everything in the glass straight away. Traces of the dissolved tablets may be left behind in the glass.

How long to take Glivec
Keep taking Glivec every day for as long as your doctor tells you.

If you take more Glivec than you should
If you have accidentally taken too many tablets, talk to your doctor **straight away**. You may require medical attention. Take the medicine pack with you.

If you forget to take Glivec
- If you forget a dose, take it as soon as you remember. However if it is nearly time for the next dose, skip the missed dose.
- Then continue with your normal schedule.
- Do not take a double dose to make up a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. They are usually mild to moderate.

Some side effects may be serious. Tell your doctor straight away if you get any of the following:

Very common (may affect more than 1 in 10 people) **or common** (may affect up to 1 in 10 people):
- Rapid weight gain. Glivec may cause your body to retain water (severe fluid retention).
- Signs of infection such as fever, severe chills, sore throat or mouth ulcers. Glivec can reduce the number of white blood cells, so you might get infections more easily.
- Unexpected bleeding or bruising (when you have not hurt yourself).

Uncommon (may affect up to 1 in 100 people) **or rare** (may affect up to 1 in 1,000 people):
- Chest pain, irregular heart rhythm (signs of heart problems).
- Cough, having difficulty breathing or painful breathing (signs of lung problems).

- Feeling light-headed, dizzy or fainting (signs of low blood pressure).
- Feeling sick (nausea), with loss of appetite, dark-coloured urine, yellow skin or eyes (signs of liver problems).
- Rash, red skin with blisters on the lips, eyes, skin or mouth, peeling skin, fever, raised red or purple skin patches, itching, burning sensation, pustular eruption (signs of skin problems).
- Severe abdominal pain, blood in your vomit, stools or urine, black stools (signs of gastrointestinal disorders).
- Severely decreased urine output, feeling thirsty (signs of kidney problems).
- Feeling sick (nausea) with diarrhoea and vomiting, abdominal pain or fever (signs of bowel problems).
- Severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness (signs of nervous system problems such as bleeding or swelling in skull/brain).
- Pale skin, feeling tired and breathlessness and having dark urine (signs of low levels of red blood cells).
- Eye pain or deterioration in vision, bleeding in the eyes.
- Pain in bones or joints (signs of osteonecrosis).
- Blisters on skin or mucous membranes (signs of pemphigus).
- Numb or cold toes and fingers (signs of Raynaud's syndrome).
- Sudden swelling and redness of the skin (signs of a skin infection called cellulitis).
- Difficulty hearing.
- Muscle weakness and spasms with an abnormal heart rhythm (signs of changes in the amount of potassium in your blood).
- Bruising.
- Stomach pain with feeling sick (nausea).
- Muscle spasms with a fever, red-brown urine, pain or weakness in your muscles (signs of muscle problems).
- Pelvic pain sometimes with nausea and vomiting, with unexpected vaginal bleeding, feeling dizzy or fainting due to low blood pressure (signs of problems with your ovaries or womb).
- Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint discomfort associated with abnormal laboratory test results (eg. high potassium, uric acid and calcium levels and low phosphorous levels in the blood).
- Blood clots in small blood vessels (thrombotic microangiopathy).

Not known (frequency cannot be estimated from the available data):
- Combination of a widespread severe rash, feeling sick, fever, high level of certain white blood cells or yellow skin or eyes (signs of jaundice) with breathlessness, chest pain/discomfort, severely decreased urine output and feeling thirsty etc. (signs of a treatment-related allergic reaction).
- Chronic renal failure.
- Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection).

If you get any of the above, **tell your doctor straight away.**

Other side effects may include:

Very common (may affect more than 1 in 10 people):
- Headache or feeling tired.
- Feeling sick (nausea), being sick (vomiting), diarrhoea or indigestion.
- Rash.
- Muscle cramps or joint, muscle or bone pain, during Glivec treatment or after you have stopped taking Glivec.
- Swelling such as round your ankles or puffy eyes.
- Weight gain.

If any of these affects you severely, **tell your doctor**.

Common (may affect up to 1 in 10 people):

- Anorexia, weight loss or a disturbed sense of taste.
- Feeling dizzy or weak.
- Difficulty in sleeping (insomnia).
- Discharge from the eye with itching, redness and swelling (conjunctivitis), watery eyes or having blurred vision.
- Nose bleeds.
- Pain or swelling in your abdomen, flatulence, heartburn or constipation.
- Itching.
- Unusual hair loss or thinning.
- Numbness of the hands or feet.
- Mouth ulcers.
- Joint pain with swelling.
- Dry mouth, dry skin or dry eye.
- Decreased or increased skin sensitivity.
- Hot flushes, chills or night sweats.

If any of these affects you severely, **tell your doctor.**

Uncommon (may affect up to 1 in 100 people):

- Painful red lumps on the skin, skin pain, skin reddening (inflammation of fatty tissue under the skin).
- Cough, runny or stuffy nose, feeling of heaviness or pain on pressing the area above the eyes or on the sides of the nose, nasal congestion, sneezing, sore throat, with or without headache (signs of upper respiratory tract infection).
- Severe headache felt as a throbbing pain or pulsing sensation, usually on one side of the head and often accompanied by nausea, vomiting and sensitivity to light or sound (signs of migraine).
- Flu-like symptoms (influenza).
- Pain or burning sensation while passing urine, increased body temperature, pain in groin or pelvic area, red- or brown-coloured or cloudy urine (signs of urinary tract infection).
- Pain and swelling of your joints (signs of arthralgia).
- A constant feeling of sadness and loss of interest, which stops you carrying out your normal activities (signs of depression).
- A feeling of apprehension and worry along with physical symptoms such as pounding heart, sweating, trembling, dry mouth (signs of anxiety).
- Sleepiness/drowsiness/excessive sleep.
- Trembling or shaky movements (tremor).
- Memory impairment.
- Overwhelming urge to move the legs (restless leg syndrome).
- Hearing noises (e.g. ringing, humming) in the ears that have no external source (tinnitus).
- High blood pressure (hypertension).
- Burping/belching.
- Inflammation of the lips.
- Difficulty swallowing.
- Increased sweating.
- Skin discolouration.
- Brittle nails.
- Red bumps or white-headed pimples around the roots of the hair, possibly with pain, itching or burning sensation (signs of inflammation of the hair follicles, also called folliculitis).
- Skin rash with flaking or peeling (exfoliative dermatitis).
- Breast enlargement (may occur in men or women).
- Dull pain and/or feeling of heaviness in the testicles or lower abdomen, pain during urination, sexual intercourse or ejaculation, blood in urine (signs of oedema of the testicles).
- Inability to get or keep an erection (erectile dysfunction).
- Heavy or irregular menstrual periods.

- Difficulty achieving/maintaining sexual arousal.
- Decreased sexual desire.
- Nipple pain.
- Generally feeling unwell (malaise).
- Viral infection such as cold sore.
- Lower back pain resulting from kidney disorder.
- Increased frequency of passing urine.
- Increase in appetite.
- Pain or burning sensation in upper abdomen and/or chest (heartburn), nausea, vomiting, acid reflux, feeling of fullness and bloating, black-coloured stools (signs of stomach ulcer).
- Joint and muscle stiffness.
- Abnormal laboratory test results.

If any of these affects you severely, **tell your doctor.**

Rare (may affect up to 1 in 1,000 people):
- Confusion.
- An episode of spasm(s) and reduced consciousness (convulsions).
- Nail discolouration.

Not known (frequency cannot be estimated from the available data):
- Reddening and/or swelling on the palms of the hands and soles of the feet which may be accompanied by tingling sensation and burning pain.
- Painful and/or blistering skin lesions.
- Slowing of growth in children and adolescents.

If any of these affects you severely, **tell your doctor.**

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Glivec

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP.
- Storage temperature
  - Glivec 100 mg film-coated tablets: Do not store above 30°C.
  - Glivec 400 mg film-coated tablets: Store below 25°C.
- Store in the original package in order to protect from moisture.
- Do not use any pack that is damaged or shows signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Glivec contains
- The active substance is imatinib mesilate.
  - Each 100 mg tablet of Glivec contains 100 mg imatinib (as mesilate).
  - Each 400 mg tablet of Glivec contains 400 mg imatinib (as mesilate).
- The other ingredients are microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate and anhydrous colloidal silica.

- The tablet coating is made of red iron oxide (E172), yellow iron oxide (E172), macrogol, talc and hypromellose.

What Glivec looks like and contents of the pack
Glivec 100 mg film-coated tablets are very dark yellow to brownish-orange round tablets. They have "NVR" on one side and "SA" and a score line on the other side.
Glivec 400 mg film-coated tablets are very dark yellow to brownish-orange oval tablets. They have "400" on one side and a score line on the other side with "SL" on each side of the score line.

Glivec 100 mg film-coated tablets are supplied in packs containing 20, 60, 120 or 180 tablets.
Glivec 400 mg film-coated tablets are supplied in packs containing 10, 30 or 90 tablets.
These may not all be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website:
http://www.ema.europa.eu