1. NAME OF THE MEDICINAL PRODUCT

ALVOTINIB 100 mg film-coated tablets
ALVOTINIB 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

100 mg film-coated tablet:
Dark yellow to brownish-orange, round shaped, film-coated tablets of 10.1 mm (± 5%) diameter with a break-line on one side and '100' on the other side. The tablet can be divided into equal doses.

400 mg film-coated tablets:
Dark yellow to brownish-orange, ovaloid shaped, film-coated tablets, 21.6 mm long & 10.6mm wide (± 5%) with a break-line on one side and '400' on the other side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imatinib is indicated for the

- treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) (for paediatric use see section 4.2).
- treatment of adult and paediatric patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy (for paediatric use see section 4.2).
- treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
- treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- treatment of adult patients with Kit+ (CD117) unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- adjuvant treatment of adult patients following complete gross resection of Kit+ GIST.

The effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, and on haematological and cytogenetic response rates in relapsed or refractory adult Ph+ ALL, ALL, on objective response rates in unresectable and/or metastatic GIST and on recurrence free survival in adjuvant GIST (see section 5.1). Except in newly diagnosed chronic phase CML there are no controlled trials demonstrating increased survival.

4.2 Posology and method of administration

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

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

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

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

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

Posology for CML

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

The prescribed dose should be administered orally, once daily with a meal and a large glass of water.

Dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-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.

Dosing in children should be on the basis of body surface area (mg/m^2). The recommended dose of imatinib for children with newly diagnosed Ph+ CML is 340 mg/m^2/day (not to exceed 600mg). Doses of 260 mg/m^2/day and 340 mg/m^2/day are recommended for children with chronic phase CML and advanced phase CML respectively, after failure of interferon-alpha therapy. However, the total daily dose in children should not exceed adult equivalent doses of 400 mg and 600 mg respectively. 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. There is no experience with the treatment of children below 2 years of age.

Posology for Ph+ ALL

The recommended dose of imatinib is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL. See section on special populations for children.

Dosing in children should be on the basis of body surface area (mg/m^2). The recommended dose of imatinib to be given in combination with chemotherapy to children with newly diagnosed Ph+ALL is 340 mg/m^2/day (not to exceed 600mg). Treatment can be given as a once daily dose. The dose recommendation is currently based on a small number of paediatric patients. See section on special populations for children.

Dosage in GIST

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

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

Treatment with imatinib in GIST patients should be continued until disease progression.

The recommended dose of imatinib 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.

Dose adjustment for adverse reactions

Non-haematological adverse reactions

If a severe non-haematological adverse drug reaction develops with imatinib 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 × institutional upper limit of normal (IULN) or in liver transaminases > 5 × IULN occur, imatinib should be withheld until bilirubin levels have returned to < 1.5 × IULN and transaminase levels to < 2.5 × IULN. Treatment with imatinib 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 260 to 200 mg/m^2/day or 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.

Table 1 Dose adjustments for neutropenia and thrombocytopenia

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

		resume imatinib at reduced dose of 300 mg.
Paediatric newly diagnosed chronic phase CML (starting dose 340 mg/m^2)	ANC < 1.0 × 10^9/l and/or platelets < 50 × 10^9/l	1. Stop imatinib until ANC ≥ 1.5 × 10^9/l and platelets ≥ 75 × 10^9/l. 2. Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 ×10^9/l and/or platelets < 50 × 10^9/l, repeat step 1 and resume imatinib at reduced dose of 260 mg/m^2.
Paediatric chronic phase CML after failure of interferon (starting dose 260 mg/m^2)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with imatinib 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 imatinib at reduced dose of 200 mg/m^2.
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	[a]ANC < 0.5 × 10^9/l and/or platelets < 10 × 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 imatinib 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 imatinib until ANC ≥ 1 × 10^9/l and platelets ≥ 20 × 10^9/l, then resume treatment at 200 mg/m^2.
Accelerated phase CML and blast crisis CML and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 × 10^9/l and/or platelets < 10 × 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 imatinib 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 imatinib until ANC ≥ 1 × 10^9/l and platelets ≥ 20 × 10^9/l, then resume treatment at 300 mg.

ANC = absolute neutrophil count

[a] occurring after at least 1 month of treatment

Special populations

Paediatric patients(below 18 years)

There is no experience with the use of imatinib in children with CML below 2 years of age and with Ph+ALL below 1 year of age.

Dosing in pediatric patients should be on the basis of body surface are (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase CML and Ph+ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML

and Ph+ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening (see section 5.2).

Hepatic impairment

Imatinib is mainly metabolised by the liver. Patients with mild or moderate liver impairment should be given the minimum recommended dose of 400 mg daily, and patients with severe liver dysfunction should start at 300 mg daily. The dose can be reduced if not tolerated (see sections 4.4, 4.8 and 5.2).

Renal impairment

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose (see section 5.2). 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).

Elderly (65 years or above)

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

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 imatinib is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking imatinib with rifampicin or other strong CYP3A4 inducers, ketoconazole or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives) (see section 4.5).

Hypothyroidism

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

Hepatotoxicity

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2, 4.8 and 5.2).

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.8).

Fluid retention

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

Patients with cardiac disease or renal failure

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported in patients taking imatinib. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomised phase 3 study in 1106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking imatinib compared to 0.9% of patients taking IFN + Ara-C. 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. Myelodysplastic (MDS)/myeloproliferative diseases (MPD) and systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

In the phase III GIST studies in patients with unresectable or metastatic malignant GIST 211 patients (12.9%) reported Grade 3/4 haemorrhage at any site. In the Phase II GIST study in patients with unresectable or metastatic malignant GIST (study B2222), eight patients (5.4%) were reported to have had gastrointestinal (GI) haemorrhage and four patients (2.7%) were reported to have had haemorrhages at the site of tumour deposits. The tumour haemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumour lesions. GI sites of tumour may have contributed to reports of GI bleeding in this patient population. In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with imatinib. When needed, imatinib discontinuation may be considered (see section 4.8).

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS) have been reported in patients treated with imatinib. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of imatinib (see section 4.8).

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as imatinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.8).

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

Laboratory tests

Complete blood counts must be performed regularly during therapy with imatinib. Treatment of CML patients with imatinib has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with imatinib may be interrupted or the dose be reduced, as recommended in section 4.2.

Liver function

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib. As recommended in section 4.2, non-haematological adverse drug reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with imatinib.

Renal Function

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics. In patients with impaired renal function, 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. As well there is a significant correlation in the incidence of serious adverse events with decreased renal function (p=0.0096). Patients with mild or moderate renal impairment should be treated with caution. Since the effect of imatinib treatment on patients with severe renal dysfunction or on dialysis has not been sufficiently assessed, recommendations on the treatment of these patients with imatinib cannot be made.

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

Paediatric patients (below 18 years)

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

Renal Toxicity

A decline in renal function may occur in patients receiving imatinib. Median estimated glomerular filtration rate (eGFR) values in patients on imatinib 400 mg daily for newly-diagnosed CML (four randomized trials) and malignant GIST (one single-arm trial) declined from a baseline value of 85 ml/min/1.73m^2 (N=1190) to 75 ml/min/1.73m^2 at 12 months (N=1082) and 69 ml/min/1.73m^2 at 60

months (N=549). Evaluate renal function prior to initiating imatinib and monitor during therapy, with attention to risk factors for renal dysfunction such as pre-existing renal impairment, diabetes mellitus, hypertension, and congestive heart failure.

4.5 Interaction with other medicinal products and other forms of interaction

Observed interactions resulting in a concomitant use not recommended

Drugs that may decrease imatinib plasma concentrations

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

Other interactions that may affect exposure to imatinib or other drugs

Drugs that may increase imatinib plasma concentrations

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

Drugs that may have their plasma concentration altered by imatinib

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 imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imatinib 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.).

Imatinib also inhibits CYP2C9 and CYP2C19 activity *in vitro*. PT prolongation was observed following co-administration with warfarin. Patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23%. Dose adjustments do not seem to be necessary when imatinib is co-administered 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, imatinib inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 microM). A non-randomized, open-label study was conducted to investigate the effects of imatinib at steady state on the pharmacokinetics of paracetamol in patients with newly diagnosed, previously untreated CML in chronic phase. Co-administration of imatinib (400 mg/day for eight days) with paracetamol (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of paracetamol. Imatinib pharmacokinetics were not altered in the presence of paracetamol.

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

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of childbearing potential must be advised to use highly effective contraception during treatment. Highly effective contraception is a method of birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). There are no clinical trials on the use of imatinib in pregnant women. There have been post-market reports of spontaneous abortions and infant congenital anomalies from women who have taken imatinib. Imatinib 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

Both imatinib and its active metabolite can be distributed into human milk. The effects of low-dose exposure of the infant to imatinib are unknown, because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 15 days after stopping treatment with imatinib. The milk plasma ratio was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and of the metabolite and the maximum daily milk intake by infants the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking imatinib should not breast-feed.

Fertility

Females

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

Infertility

Human studies on male patients receiving imatinib and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on imatinib treatment should consult with their physician Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperm were observed in the high dose males rats. In pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by imatinib.

4.7 Effects on ability to drive and use machines

Reports of motor vehicle accidents have been received in patients receiving imatinib. While most of these reports are not suspected to be caused by imatinib, 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 events difficult to assess due to the variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medicinal products.

Imatinib was generally well tolerated with chronic oral daily dosing in patients with CML including paediatric patients. The majority of adult patients experienced adverse events at some point in time, but most were of mild to moderate grade, and in clinical trials drug discontinuation for drug-related adverse events 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 the GIST study (B2222), imatinib was discontinued for drug-related adverse reactions in 4% of patients.

The adverse reactions were similar in all indications, with two exceptions. There was less myelosuppression in GIST and intra-tumoural haemorrhage was only seen in the GIST population (see section 4.4). The most frequently reported drug-related adverse events were mild nausea, vomiting, diarrhoea, myalgia, muscle cramps and rash, which were easily manageable. 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 in some patients by reducing the dose of imatinib.

Overall, the incidence of all grades of adverse reactions and the incidence of severe adverse reactions were similar between the 400mg and 800mg treatment groups except for oedema, which was reported more frequently in the 800mg group in the phase III studies in patients with unresectable or metastatic malignant GIST (SWOG, EORTC studies).

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.

Miscellaneous adverse events such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as “fluid retention”. These events can usually be managed by withholding imatinib temporarily and/or with diuretics and/or other appropriate supportive care measures. However, a few of these events may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure.

Adverse reactions (Table 2 and Table 3) are ranked under heading of frequency, the most frequent first, 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), including isolated reports. Adverse reactions and their frequencies reported in Table 2 are based on the registration studies for CML and GIST.

Table 2 Adverse reactions in clinical studies for CML and GIST

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

Uncommon:	Hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[8], hepatic necrosis[8]
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
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very common:	Muscle spasm and cramps, musculoskeletal pain including myalgia[10], arthralgia, bone pain[9]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis
Renal and urinary disorders	
Uncommon:	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased

Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

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

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

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

[4] Flushing was most common in GIST patients and bleeding (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 and related events were more commonly observed in patients with CML than in GIST patients.

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

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

Table 3 Adverse reactions from post-marketing reports

Infections and infestations	
Not known:	Hepatitis B reactivation
Nervous system disorders	
Uncommon:	Cerebral oedema
Eye disorders	
Rare:	Vitreous haemorrhage
Cardiac disorders	
Rare:	Pericarditis, cardiac tamponade
Vascular disorders	
Uncommon:	Thrombosis/embolism
Very rare:	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Uncommon:	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation[2]
Rare:	Diverticulitis, gastric antral vascular ectasia (GAVE)
Skin and subcutaneous tissue disorders	
Uncommon:	Palmar-plantar erythrodysaesthesia syndrome
Rare:	Lichenoid keratosis, lichen planus
Very rare:	Toxic epidermal necrolysis

Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)
Rare:	Avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy
Not known:	Growth retardation in children
Reproductive disorders	
Very rare:	Hemorrhagic corpus luteum / hemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour Lysis Syndrome

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

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

Description of selected Adverse Drug Reactions

Myelosuppression

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

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

Haemorrhage

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

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

Oedema and Fluid Retention

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

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

Skin Rashes and Severe Cutaneous Adverse Reactions

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

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

Hepatotoxicity

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

Hypophosphataemia

Low serum phosphate and hypophosphataemia (up to Grade 3 or 4) has been observed relatively commonly across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of imatinib. Sustained inhibition of osteoclastic activity may lead to counter regulatory response resulting in

increased levels of PTH. The clinical relevance of the preclinical findings is yet unclear and an association with skeletal AEs such as bone fractures has not been demonstrated.

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

Gastrointestinal Obstruction, Perforation or Ulceration

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

Tumour lysis syndrome

A causal relationship between tumour lysis syndrome and imatinib treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks (see section 4.4).

Growth retardation in children

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

Severe respiratory adverse drug reaction

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

Laboratory test abnormalities

Haematology

In CML-associated cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses $\geq$750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients. The frequency of Grade 3 or 4 neutropenias (ANC $< 1.0 \times 10^9$/l) and thrombocytopenias (platelet count $< 50 \times 10^9$/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59 to 64% and 44 to 63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). In newly diagnosed chronic phase CML Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/l) and thrombocytopenia (platelet count $< 10 \times 10^9$/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 dose reduction or an interruption of treatment with imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were Grade

3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

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

Biochemistry

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

4.9 Overdose

Experience with higher than therapeutic doses is limited. Isolated cases of imatinib overdosage have been reported spontaneously and in the literature. Generally, the reported outcome in these cases was improvement or recovery. In the event of overdosage the patient should be observed and appropriate symptomatic treatment should be given. Events that have been reported at different dose ranges are as follows:

Adult overdose

1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain.

6,400 mg (single dose): One case 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 overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protein-tyrosine kinase inhibitor, 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 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 breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase at the *in vitro*, cellular, *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients. In colony transformation assays using ex vivo peripheral blood and bone marrow samples, imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients.

In vivo the compound shows anti-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) and stem cell factor (SCF), KIT, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating kit mutation. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, KIT and ABL kinase activity.

5.2 Pharmacokinetic properties

Pharmacokinetics of imatinib

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

Distribution

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

Metabolism

The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP 71588), which shows similar *in vitro* potency as the parent compound. The plasma AUC for this metabolite was

found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Elimination

Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in 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.

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

Plasma pharmacokinetics

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

Population pharmacokinetics

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

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

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

Based on pooled population pharmacokinetic analysis in 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, 4.4 and 5.1).

Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not differ significantly between patients with mild and moderate liver dysfunction (as measured by dose normalized AUC) and patients with normal liver function. Patients with severe liver dysfunction demonstrated increased exposure to imatinib. (see sections 4.2, 4.4, 4.8, 5.1 and 5.2 'Pharmacokinetics').

CLINICAL STUDIES

Clinical studies in CML

The effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression free survival.

Three large, international, open-label, non-controlled phase II studies were conducted in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (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, multicenter, international randomized phase III study has been conducted in patients with newly diagnosed Ph+ CML. In addition, children have been treated in two phase I studies and one phase II study.

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

Chronic phase, newly diagnosed:

This phase III study in adult patients compared treatment with either single-agent imatinib at 400mg daily or a combination of 5 MIU/m^2/day IFN and 20 mg/m^2/day Ara-C for 10 days/month, both subcutaneously. Patients showing lack of response (lack of complete haematological response (CHR) at 6 months, increasing white blood cells (WBC), no major cytogenetic response (MCyR) at 24 months), loss of response (loss of CHR or MCyR) or severe intolerance to treatment were allowed to crossover to the alternative treatment arm. A total of 1,106 patients were randomized, 553 to each arm. Median age was 51 years (range 18 to 70 years), with 21.9% of patients ≥60 years of age. 59% males and 41% females; At the 7 year follow up, the median duration of first-line treatment was 82 and 8 months in the imatinib and IFN arm, respectively. The median duration of second-line treatment with imatinib was 64 months. Overall, in patients receiving first line imatinib, 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 (AP/BC), death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. Major cytogenetic response, haematological response, molecular response (evaluation of minimal residual disease), time to accelerated phase or blast crisis and survival are main secondary endpoints. Response data are shown in Table 4.

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

(Best response rates)	**Imatinib** 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 (%)	40*	2*
Major response at 24 months (%)	54	NA**

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

**insufficient data, only two patients available with samples

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

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

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

Major molecular response criteria: in the peripheral blood, reduction 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 imatinib 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 imatinib arm: 37 (6.7%) involving progression to AP/BC, 31 (5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in WBC and 10 (1.8%) CML unrelated deaths. In contrast, there were 165 (29.8%) events in the IFN+Ara-C arm of which 130 occurred during first-line treatment with IFN+Ara-C.

The estimated rate of patients free of progression to accelerated phase or blast crisis at 84 months was significantly higher in the imatinib arm compared to the IFN arm (92.5% versus 85.1%, $p<0.001$). The annual rate of progression to AP or BC 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 imatinib arm and 60.6% in the control arm ($p<0.001$). The yearly rates of progression of any type for imatinib also decreased over time.

A total of 71 (12.8%) and 85 (15.4%) patients died in the imatinib and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80, 87) in the randomized imatinib 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 imatinib. The effect of imatinib treatment on survival in chronic phase, newly diagnosed CML has been further examined in a retrospective analysis of the above reported imatinib 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 imatinib over IFN+Ara-C in overall survival was demonstrated ($p<0.001$); within 42 months, 47 (8.5%) imatinib 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 imatinib. Whereas an estimated 96% (93%) of patients with CCyR (PCyR) at 12 months were free of progression to AP/BC at 84 months, only 81% of patients without MCyR at 12 months were free of progression to advanced CML at 84 months ($p<0.001$ overall, $p=0.25$ between CCyR and PCyR). For

patients with CCyR and reduction in Bcr-Abl transcripts of at least 3 logarithms at 12 months, the probability of remaining free from progression to AP/BC was 100% at 60 months. Similar findings were found based on a 18-month 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 ADRs was higher in the 40 patients in whom the dose was increased to 800 mg daily compared to the population of patients before dose increase (n=551). The more frequent ADRs included gastrointestinal haemorrhages, conjunctivitis and elevation of transaminases or bilirubin. Other ADRs were reported with lower or equal frequency.

Chronic phase, Interferon-failure: 532 patients were treated at a starting dose of 400 mg. The patients were distributed in three main categories: 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 $\geq 25 \times 10^6$ IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. The primary efficacy variable of the study was the rate of major cytogenetic response (complete plus partial response, 0 to 35 % Ph+ metaphases in the bone marrow).

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

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

The primary efficacy variable was the rate of haematological response, reported as either CHR, 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. Importantly, 27.7% of patients also achieved a MCyR, 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 ("pre-treated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the rate of haematological response, reported as either CHR, no evidence of leukaemia, or return to chronic phase CML.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 5 Response in CML

	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%	20.4%	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 × 10^9/l, platelets <450 × 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 × 10^9/l, platelets ≥100 × 10^9/l, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: Same criteria as for CHR but ANC ≥1 × 10^9/l and platelets ≥20 × 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 patients

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 imatinib 340 mg/m^2/day, with no interruptions in the absence of dose limiting toxicity. Imatinib treatment induced a rapid response in newly diagnosed paediatric CML patients with a CHR of 78% after 8 weeks of therapy. The high rate of CHR was 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.

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

Clinical studies in newly diagnosed Ph+ ALL

Paediatric patients: 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, multicenter, sequential cohort, non-randomized phase III trial, and were treated with imatinib (340 mg/m^2/day) in combination with intensive chemotherapy after induction therapy. Imatinib was administered intermittently in cohorts 1 to 5, with increasing duration and earlier start of imatinib from cohort to cohort; cohort 1 receiving the lowest intensity and cohort 5 receiving the highest intensity of imatinib (longest duration in days with continuous daily imatinib dosing during the first chemotherapy treatment courses). Continuous daily exposure to imatinib 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 imatinib (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.

Clinical studies in relapsed/refractory Ph+ ALL

When imatinib was used as single agent in patients with relapsed/refractory Ph+ ALL, it resulted, in the 66 out of 429 patients evaluable for response, in a haematological response rate of 33% (12% complete) and a major cytogenetic response rate of 23%. The median time to progression in the overall population of 429 patients with relapsed/refractory Ph+ ALL ranged from 1.96 to 3.1 months, and median overall survival in the 409 evaluable patients ranged from 5 to 9 months. The data was similar when re-analysed to include only those patients age 55 or older.

Clinical studies in unresectable or metastatic GIST

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

The primary objective of the two studies was to evaluate either progression free survival (PFS) with a secondary objective of overall survival (OS) in one study (EORTC) or overall survival with a secondary objective of PFS in the other study (SWOG). A planned analysis of both OS and PFS from the combined datasets from these two studies was conducted. Results from this combined analysis are shown in Table 6.

Table 6 Overall survival, Progression Free Survival and Tumour Response Rates in the Phase III GIST Trials

	Imatinib 400 mg N=818	**Imatinib 800 mg N=822**
Progression Free Survival (months) (50% median) [95% CI]	18.9 [17.4-21.2]	23.2 [20.8-24.9]
Overall Survival (months) [95% CI]	49.0 [45.3-60.0]	48.7 [45.3-51.6]
Best Overall Tumour Response Complete Response (CR) Partial Response (PR)	43 (5.3%) 377 (46.1%)	41 (5.0%) 402 (48.9%)

Median follow up for the combined studies was 37.5 months. There were no observed differences in OS between the treatment groups (p=0.98). Patients who crossed over following disease progression from the 400 mg/day treatment group to the 800 mg/day treatment (n=347) had a 3.4 month median and 7.7 month mean exposure to imatinib following crossover.

One phase II, open-label, randomized multinational study was conducted in patients with Kit (CD117) positive unresectable or metastatic GIST. In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally daily for up to 36 months. The primary outcome of the study was objective response rates. Tumours were required to be measurable in at least one site of disease, and response characterization was based on Southwestern Oncology Group (SWOG) criteria.

There were no differences in response rates between the two dose groups. The response rate was 68.5% for the 400 mg group and 67.6% for the 600 mg group. The median time to response was 12 weeks (range was 3-98 weeks) and the estimated median duration of response is 118 weeks (95% CI: 86, not reached)

Clinical studies in adjuvant GIST

In the adjuvant setting, imatinib 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 histologic diagnosis of primary GIST expressing KIT protein by immunochemistry and a tumour size ≥3 cm in maximum dimension, with complete gross resection of primary GIST within 14 to 70 days prior to registration. After resection of primary GIST, patients were randomized to one of the two arms: imatinib at 400 mg/day or matching placebo for one year.

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

Based on an interim analysis at a median follow-up of 14.0 months, imatinib prolonged significantly RFS with 75% of patients being recurrence-free at 38 months in the imatinib group vs 20 months in the placebo group (95% CIs, [30 non-estimable]; [14 non-estimable], respectively); (hazard ratio = 0.398 [0.259 to 0.610], p<0.0001). At one year the overall RFS was significantly better for imatinib (97.7%) vs. placebo (82.3%), (p<0.0001) therefore reducing the risk of recurrence by approximately 89% as compared with placebo (hazard ratio = 0.113 [0.049 to 0.264]). The current follow-up is too short to evaluate survival.

The risk of recurrence in patients after surgery of their primary GIST was retrospectively assessed based on the following prognosis factors: tumour size, mitotic index, tumour location. Mitotic index data were available for 556 of the 773 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 the table 7 below.

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

					RFS rates (%)	
Risk criteria	**Risk level**	**% of patients**	**No. of events/ No. of patients**	**Overall hazard ratio (95% CI)***	**12 month**	**24 month**
			Imatinib vs placebo		**Imatinib vs placebo**	**Imatinib 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 estimate

A second open label phase III study (SSG XVIII/AIO) compared 400 mg/day imatinib 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 was a total of 397 patients consented and randomized to the study (199 patients on 12 month arm and 198 patients on 36 month arm), median age was 61 years (range 22 to 84 years). The median time of follow-up was 54 months (from date of randomization to data cut-off), with a total of 83 months between the first patient randomized and the cut-off date.

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

Thirty-six (36) months of imatinib treatment significantly prolonged RFS compared to 12 months of imatinib treatment (with overall Hazard Ratio (HR)=0.46 [0.32, 0.65], p<0.0001 and a HR of 0.42 [0.28, 0.61] beyond month 12) (Table 8, Figure 1). There were 84 (42%) and 50 (25%) total RFS events for the 12-months and 36 months arms respectively.

In addition, thirty-six (36) months of imatinib treatment significantly prolonged overall survival (OS) compared to 12 months of imatinib treatment (HR=0.45 [0.22, 0.89], p=0.0187) (Table 8, Figure 2). The total number of deaths were 25 for the 12-months treatment arm and 12 for the 36-months treatment arm.

Table 8 12-month and 36-month Imatinib Treatment (SSGXVIII/AIO Trial)

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

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

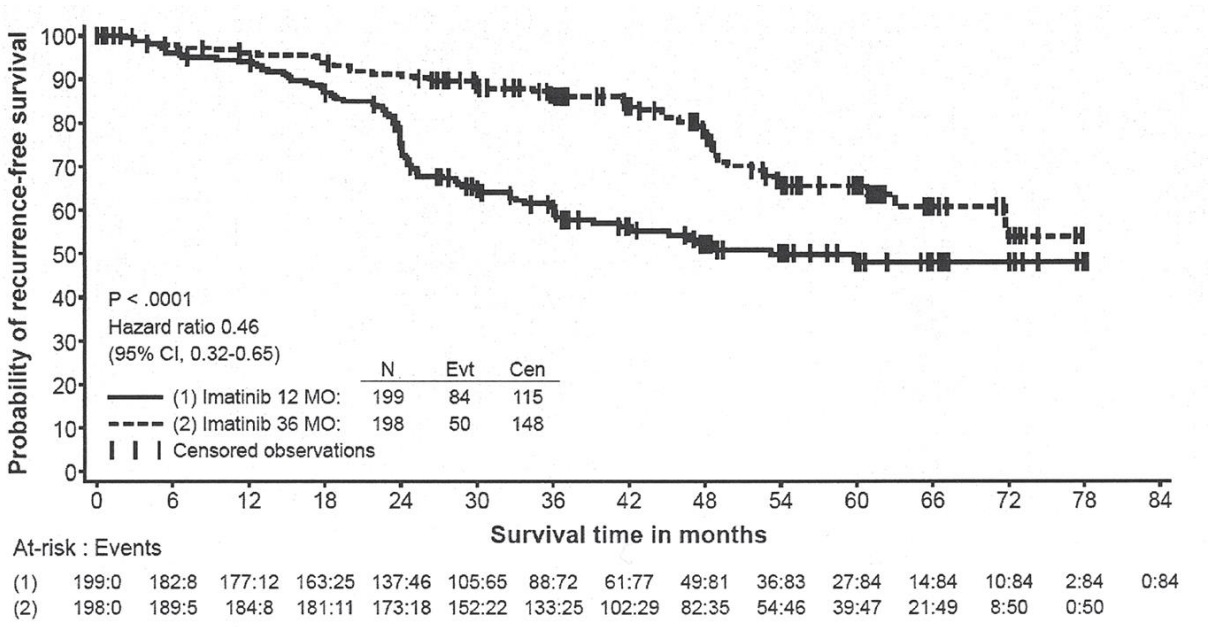
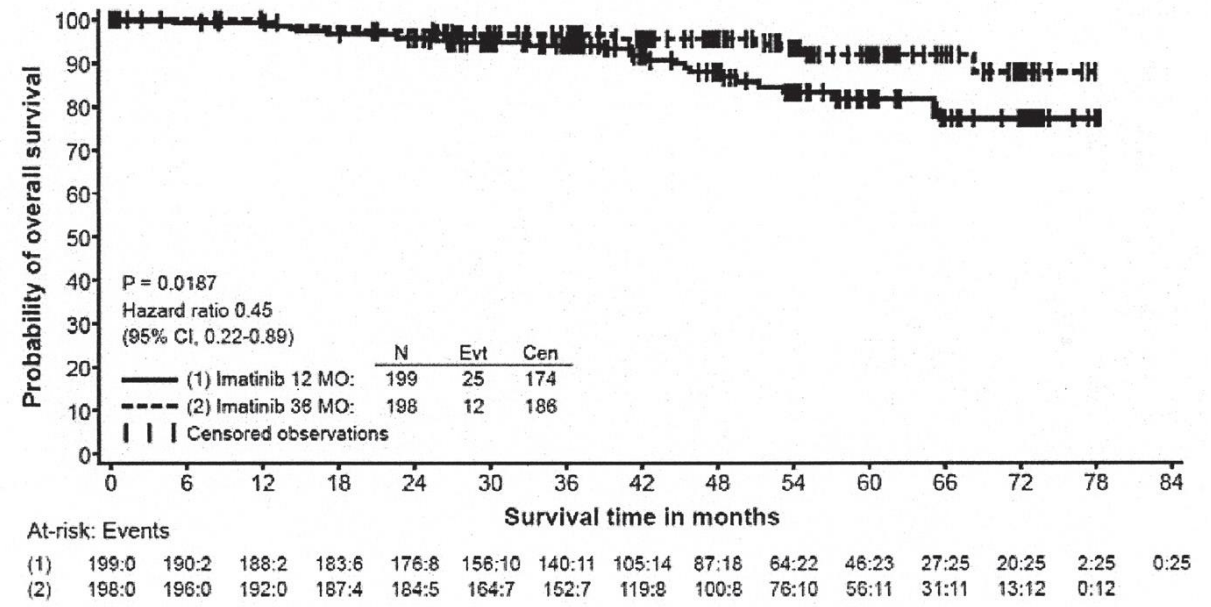


Figure 2 Kaplan-Meier estimates for overall survival (ITT population)



Clinical studies in hepatic insufficiency

In a study of patients with varying degrees of hepatic dysfunction (mild, moderate and severe - see Table 9 below for liver function classification), the mean exposure to imatinib (dose normalized AUC) showed similar exposure between patients with mild and moderate impairment, but an approximately 45% higher exposure in patients with severe impairment.

In this study, 500 mg daily was safely used in patients with mild liver impairment and 300 mg daily was used in other patients. Although only a 300 mg daily dose was used in patients with moderate and severe liver impairment, pharmacokinetic analysis projects that 400 mg can be used safely in patients with moderate liver impairment, and a dose of 300 mg can be used for patients with severe liver impairment. Imatinib should be given with caution in patients with liver impairment. (see sections 4.2, 4.4, 4.8 and 5.2).

Table 9 Liver function classification

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

ULN=upper limit of normal for the institution

SGOT = serum glutamic oxaloacetic transferase

Clinical studies in renal insufficiency

In a study of patients with varying degrees of renal dysfunction (mild, moderate and severe - see Table 10 below for renal function classification), the mean exposure to imatinib (dose normalized AUC) increased 1.5 to 2 fold compared to patients with normal renal function, which corresponded to an elevated plasma level of AGP, a protein to which imatinib binds strongly. There was a correlation with the incidence of serious adverse events and decreasing renal function (p=0.0096). In this study, 800 mg daily was safely used in patients with mild renal dysfunction and 600 mg daily was used in moderate renal dysfunction. The 800 mg dose was not tested in patients with moderate renal dysfunction due to the limited number of patients enrolled. Similarly, only 2 patients with severe renal dysfunction were enrolled at the low (100 mg) dose, and no higher doses were tested. No patients on haemodialysis were enrolled in the study. Since the efficacy of imatinib treatment on patients with severe renal dysfunction and on haemodialysis has not been sufficiently assessed, treatment of these patients with imatinib cannot be recommended. Patients with mild or moderate renal dysfunction should be treated with caution, and be given the minimum recommended dose of 400mg daily as starting dose. The dose should be reduced if not tolerable, or increased for lack of efficacy. Dosing of patients with moderate renal insufficiency at 800 mg cannot be recommended as this has not been investigated.

Table 10 Renal function classification

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

CrCL = Creatinine Clearance

5.3 Preclinical safety data

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

Imatinib was embryotoxic and teratogenic in rats. Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperm were observed in the high dose male rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by imatinib.

No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 post-partum). In the juvenile toxicology study, transitory effects upon growth and delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m^2. Also, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average 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. The no observed effect levels (NOEL) for the various target organs with neoplastic lesions were established as follows: 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach, and 15 mg/kg/day for the preputial and clitoral gland.

The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0.5 to 4 or 0.3 to 2.4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 to 3.0 times the daily exposure in children (based on AUC) at 340 mg/m^2. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose (E460)

Low substituted hydroxypropyl cellulose (E463)

Povidone (E1201)

Crospovidone (Type A) (E1202)

Silica colloidal anhydrous (E551)

Magnesium stearate (E572)

Tablet coat:

Hypromellose (E464)
Macrogol 400
Talc (E553b)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

See folding box.

6.4 Special precautions for storage

See folding box.

6.5 Nature and contents of container

PVC/PE/PVDC/Alu blisters

Packs containing
10, 20, 30, 60, 90, 120, 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

8. DATE OF REVISION OF THE TEXT

07/2021