SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMATIS 400 mg film coated tablets
Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Active substance:
Imatinib…….....400 mg (equivalent to 478 mg imatinib mesylate)
Excipients:
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets
Very dark yellow to brownish-orange colored, capsule-shaped, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMATIS is indicated for the

- treatment of patients with newly diagnosed Philadelphia chromosome positive chronic phase chronic myeloid leukemia (CML),
- treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in accelerated phase,
- treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast phase,
- treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) who are resistant to other therapies,
- treatment of patients with chronic myeloid leukemia (CML) in chronic/accelerated/blast phase who were initially diagnosed with Philadelphia chromosome positive chronic myeloid leukemia (CML) that has, however, become Philadelphia chromosome negative due to the treatment,
- first-line treatment of children at and over 3 years of age with chronic myeloid leukemia (CML),
- the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- the adjuvant treatment in adult patients who are at high risk** according to AFIP* criteria of relapse following resection of Kit (CD117)-positive GIST, for three years.
- remission induction of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) in combination with multi-agent chemotherapy regimen, shown clinical benefit,
- remission induction of patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) in combination with multi-agent chemotherapy regimen, shown clinical benefit,
- treatment of patients with hypereosinophilic syndrome and systemic mastocytosis which the

FIP1Ll-PDGFRA fusion gene was demonstrated by laboratory investigations.
(*Armed Forces Institute of Pathology (AFIP) criteria are given in section 5.1 Pharmacodynamic properties.
**Definition of high-risk groups according to AFIP criteria;
1- Those with a tumor size of more than 6 cm and a mitotic index of more than 5 in areas located in the stomach
2- Those with a tumor size of 10 cm or more or with a mitotic index of more than 5 in locations other than the stomach)

4.2 Posology and method of administration

Posology/frequency and duration of administration:

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

Treatment should be continued as long as the patient benefits.

Posology for chronic myeloid leukemia (CML)

The recommended dosage of IMATIS 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 >100×10^9/L.

The recommended dosage of IMATIS 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 <100×10^9/L unrelated to therapy.

The recommended dose of IMATIS 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.

Dose increases from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg in patients with accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe leukemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response.

Posology for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)

The recommended dose of IMATIS for patients with Ph+ALL is determined based on the remission induction chemotherapy regimen.

Posology for hypereosinophilic syndrome and systemic mastocytosis

The recommended dose of IMATIS is 100 mg/day for patients with hypereosinophilic syndrome and systemic mastocytosis. Dose increase to 400 mg may be considered in the absence of response to therapy. This dose cannot be exceeded.

Posology for gastrointestinal stromal tumors (GIST)

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

If assessments reveal an inadequate response to therapy, a dose increase from 400 mg to 600 mg or

800 mg may be considered in patients without adverse drug reactions.

The recommended duration of treatment is 36 months. In the adjuvant setting setting, the optimal duration of treatment with IMATIS is unknown.

The recommended dose of IMATIS for the adjuvant treatment of adult patients following GIST resection is 400 mg/day. The recommended duration of treatment is 36 months. The optimal duration of treatment with imatinib is not yet established in the adjuvant treatment setting,

Dose adjustment for adverse reactions

Non-hematological adverse reactions
If a severe non-hematological adverse reaction develops with IMATIS 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, IMATIS should be withheld until bilirubin levels have returned to <1.5×IULN and transaminase levels to <2.5×IULN. Treatment with IMATIS 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 mg/m^2/day to 200 mg/m^2/day or from 340 mg/m^2/day to 260 mg/m^2/day.

Hematological 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:

SM associated with eosinophilia and HES with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC <1.0×10^9/L and/or platelets <50 ×10^9/L	1. Stop IMATIS treatment until ANC ≥1.5×10^9/L and platelets ≥75×10^9/L. 2. Resume treatment with IMATIS at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, SM, HES (starting dose 400 mg)	ANC <1.0×10^9/l and/or platelets <50×10^{99}/l	1. Stop IMATIS treatment until ANC ≥1.5×10^9/L and platelets ≥75×10^9/L. 2. Resume treatment with IMATIS 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 IMATIS at reduced dose of 300 mg.
Pediatric chronic phase CML (at dose 340 mg/m^2)	ANC <1.0×10^9/L and/or platelets <50×10^9/L	1. Stop IMATIS treatment until ANC ≥1.5×10^9/L and platelets ≥75×10^9/L. 2. Resume treatment with IMATIS 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 IMATIS treatment at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ALL (starting dose 600 mg)	[a]ANC <0.5×10^9/l and/or platelets <10×10^9/l	1. Check whether cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, reduce dose of IMATIS to 400 mg.

		3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop IMATIS treatment until ANC $\geq 1\times10^9$/L and platelets $\geq 20\times10^9$/L, then resume treatment at 300 mg.
ANC=absolute neutrophil count [a]occuring after at least 1 month of treatment		

Method of administration
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the gastrointestinal side effects. 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 mineral 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).

Additional information on special population
Hepatic insufficiency
Imatinib is mainly metabolized 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, 5.1, 5.2).

Renal insufficiency
Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis could be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated, or increased for lack of efficacy (see section 4.4).

Pediatric population
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. There is very limited experience with the use of imatinib in children in other indications.

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

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 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 or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening in CML (see section 5.1).

Geriatric population
Imatinib pharmacokinetics has not been specifically studied in the elderly.
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.

4.4 Special warnings and precautions for use
When IMATIS is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking IMATIS 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 IMATIS, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).

One patient who was taking paracetamol (acetaminophen) regularly for fever died of acute liver failure. Although the etiology is currently unknown, special caution should be exercised when using paracetamol/acetaminophen (see section 4.5).

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

Hepatotoxicity:
Imatinib is primarily metabolized in the liver and only 13% of excretion is via 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, 5.1 and 5.2). It is possible for patients with GIST to have liver metastases that can lead to liver failure.

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. 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 4.5 and 4.8).

Fluid retention:
Occurrences of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, superficial edema) have been reported in approximately 2.5% of newly diagnosed CML patients taking imatinib. 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 elderly patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

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

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of 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, a careful assessment of the benefit/risk of IMATIS therapy should be considered before treatment initiation in the HES/CEL (chronic eosinophilic leukemia) population as uncommon cardiac adverse events have been reported. Myelodysplastic/myeloproliferative diseases (MDS/MPD) and systemic mastocytosis might 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 MDS/MPD, and in patients with HES or SM (systemic mastocytosis) associated with high eosinophil levels. If either is abnormal, follow-up with a cardiology specialist and 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 hemorrhage:
In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural hemorrhages 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 hemorrhage. 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 hemorrhage in all patients should be applied.

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

Tumor lysis syndrome:
Cases of tumor 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 IMATIS (see section 4.8).

Hepatitis B reactivation:
Reactivation of hepatitis B in patients who are chronic carriers of this Hepatitis B virus (HBV) 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 IMATIS. 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 IMATIS 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 imatinib (see section 4.8). If laboratory or clinical signs associated with TMA occur in a patient receiving IMATIS, treatment should be discontinued and a comprehensive evaluation for TMA should be performed, including determination of ADAMTS13 activity and anti-ADAMTS13-antibody. If anti-ADAMTS13-antibody is elevated with low ADAMTS13 activity, IMATIS therapy should not be restarted.

Laboratory tests:
Complete blood counts must be performed regularly during therapy with IMATIS. Treatment of CML patients with imatinib 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 IMATIS may be interrupted or the dose may be reduced, as recommended in section 4.2 Posology and method of administration.

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

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.

Pediatric population
There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. In an observational study in the CML pediatric 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. 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
Drugs that alter imatinib plasma concentrations
Drugs 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 and boceprevir; azole antifungal drugs such as ketoconazole, itraconazole, posaconazole and 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 IMATIS with inhibitors of the CYP3A4 isoenzyme.

Drugs that may decrease imatinib plasma concentrations:
Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *hypericum perforatum* also known as St. John's Wort) may significantly reduce exposure to IMATIS and increase the risk of treatment failure. Administration of multiple 600 mg pretreatment rifampicin doses followed by a single 400 mg dose of imatinib resulted in reductions in C_{max} and $AUC_{0-\infty}$ of at least 54% and 74% of the corresponding values in the absence of rifampicin therapy. Similar results were observed also in patients with malignant gliomas treated with imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbazepine, oxcarbazepine, and phenytoin. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong inducers of CYP3A4 with imatinib should be avoided.

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 IMATIS with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine). IMATIS may increase plasma concentration of CYP3A4 metabolised other 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. hemorrhage), patients who require anticoagulation should receive low-molecular-weight or standard heparin, instead of coumarin derivatives such as warfarin.

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% (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, imatinib inhibits paracetamol O-glucuronidation with K_i value of 58.5 µmol/l. This inhibition has not been observed *in vivo* after the administration of imatinib 400 mg and paracetamol 1000 mg. Higher doses of imatinib and paracetamol have not been studied. Caution should therefore be exercised when using high doses of IMATIS and paracetamol concomitantly.

In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when IMATIS 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 imatinib with chemotherapy (see section 5.1), but drug-drug interactions between imatinib and chemotherapy regimens are not well

characterized. 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 IMATIS in combination requires special precaution.

Additional information on special populations
No clinical interaction studies have been conducted in special populations.

Pediatric population
No clinical interaction studies have been conducted in the pediatric population.

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category is D.

Women of child-bearing potential/Contraception
Women of child-bearing potential should be advised to use effective contraception during treatment and for at least 15 days after treatment is stopped.

Pregnancy
Imatinib has harmful pharmacological effects on pregnancy and/or the fetus/newborn. IMATIS should not be used during pregnancy unless necessary. 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. IMATIS should not be used during pregnancy unless expected benefit outweighs the potential risk. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.

Breast-feeding
There is limited information on the excretion of imatinib into human milk. Studies in two breastfeeding women have revealed that both imatinib and its active metabolite can pass into breast milk. The milk plasma ratio examined 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 taking IMATIS should not breast-feed.

Reproductive ability / Fertility
Clinical studies on male patients receiving imatinib and its affect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on IMATIS treatment should consult with their physician. For preclinical studies on fertility, see the relevant section (see section 5.3).

4.7. Effects on ability to drive and use machines
Patients should be informed that they may experience undesirable effects such as dizziness, somnolence or blurred vision during treatment with imatinib. Therefore, caution should be advised when driving 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-tumoral bleeds (3 patients) or both (1 patient). GI tumor sites may have been the source of the GI bleeds (see section 4.4). GI and tumoral bleeding may be serious and sometimes fatal. The most commonly reported (≥ 10%) drug-related adverse reactions in both settings were mild nausea, vomiting, diarrhea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib.

When imatinib was combined with high dose chemotherapy in Ph+ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia 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 edema and rapid weight gain with or without superficial edema may be collectively described as “fluid retention”. These reactions can usually be managed by withholding imatinib 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 pediatric clinical trials.

Adverse reactions are ranked under headings 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); not known (cannot be estimated from the available data). The following adverse reactions and their frequencies are based on the studies conducted 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
Not known : Hepatitis B reactivation*

Benign and malignant neoplasms (including cysts and polyps)
Rare : Tumor lysis syndrome
Not known : Tumor hemorrhage/tumor necrosis*

Blood and lymphatic system disorders
Very common : Neutropenia, thrombocytopenia, anemia
Common : Pancytopenia, febrile neutropenia
Uncommon : Thrombocythemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare : Hemolytic anemia

Immune system disorders
Not known : Anaphylactic shock*

Metabolism and nutrition disorders
Common : Anorexia
Uncommon : Hypokalemia, increased appetite, hypophosphotemia, decreased appetite, dehydration, gout, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia
Rare : Hyperkalemia, hypomagnesemia

Psychiatric disorders
Common : Insomnia
Uncommon : Depression, decreased libido, anxiety
Rare : Confusional state

Nervous system disorders
Very common : Headache[2]
Common : Dizziness, paresthesia, taste disturbance, hypoesthesia
Uncommon : Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral hemorrhage
Rare : Increased intracranial pressure, convulsions, optic neuritis
Not known : Cerebral edema*

Eye disorders
Common : Eyelid edema, lacrimation increased, conjunctival hemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon : Eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema
Rare : Cataract, glaucoma, papilledema
Not known : Vitreous hemorrhage*

Ear and labyrinth disorders
Uncommon : Vertigo, tinnitus, hearing loss

Cardiac disorders
Uncommon : Palpitations, tachycardia, cardiac failure congestive[3], pulmonary edema
Rare : Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Not known : Pericarditis*, cardiac tamponade*

Vascular disorders[4]

Common : Flushing, hemorrhage
Uncommon : Hypertension, hematoma, subdural hematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Not known : Thrombosis/embolism*

Respiratory, thoracic and mediastinal disorders

Common : Dyspnea, epistaxis, cough
Uncommon : Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare : Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage
Not known : Acute respiratory failure[11]*, interstitial lung disease*

Gastrointestinal disorders

Very common : Nausea, diarrhea, vomiting, dyspepsia, abdominal pain[6]
Common : Flatulence, abdominal distension, gastro-esophageal reflux, constipation, dry mouth, gastritis
Uncommon : Stomatitis, mouth ulceration, gastrointestinal hemorrhage, eructation, melena, esophagitis, ascites, gastric ulcer, hematemesis, 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 : Hyperbilirubinemia, hepatitis, jaundice
Rare : Hepatic failure[8], hepatic necrosis

Skin and subcutaneous tissue disorders

Very common : Periorbital edema, dermatitis/eczema/rash
Common : Pruritus, face edema, 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 discoloration, angioneurotic edema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP).
Not known : Palmoplantar erythrodysesthesia syndrome*, lichenoid keratosis*, lichen planus*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS)*, pseudoporphyria*.

Musculoskeletal, connective tissue and bone disorders

Very common : Muscle spasm and cramps, musculoskeletal pain including myalgia[9], arthralgia, bone pain[10]
Common : Joint swelling
Uncommon : Joint and muscle stiffness
Rare : Muscular weakness, arthritis, rhabdomyolysis/myopathy
Not known : Avascular necrosis/hip osteonecrosis*, growth retardation in children*

Renal and urinary disorders
Uncommon : Renal pain, hematuria, renal failure acute, urinary frequency increased
Not known : Renal failure chronic

Reproductive system and breast disorders
Uncommon : Gynecomasty, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal edema
Very rare : Hemorrhagic corpus luteum/hemorrhagic ovarian cyst

General disorders and administration site conditions
Very common : Fluid retention and edema, 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 imatinib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programs, 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 (hematoma, hemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).
[5] Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
[6+7] Abdominal pain and gastrointestinal hemorrhage were most commonly observed in GIST patients.
[8] 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.

Laboratory test abnormalities
Hematology
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. 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 $<1.0\times10^9$/L) and thrombocytopenias (platelet count $<50\times10^9$/L) was 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 $<0.5\times10^9$/L) and thrombocytopenia (platelet count $<10\times10^9$/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 IMATIS, but can in rare cases lead to permanent discontinuation of treatment. In pediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy.

In the study in patients with unresectable and/or metastatic GIST (Study B2222), grade 3 and 4 anemia 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 authorization 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 national reporting system.

4.9 Overdose
Experience with doses higher than the recommended therapeutic dose is limited. Isolated cases of imatinib overdose have been reported spontaneously and in the literature. Generally the reported outcome in these cases was improved or recovered. In the event of overdose the patient should be observed and appropriate symptomatic treatment should be given.

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

Adult overdose:
1200 to 1600 mg (duration varying between 1 to 10 days):
Nausea, vomiting, diarrhea, rash, erythema, edema, swelling, fatigue, muscle spasms,

thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

1800 to 3200 mg (as high as 3200 mg daily for 6 days):
Weakness, myalgia, increased CPK, 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agent, 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 c-Kit proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor (PDGF) 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 that potently inhibits the concentration of breakpoints-Abelson (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, new leukemia cells from Philadelphia chromosome positive CML and ALL patients.

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

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), 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. In addition, constitutive activation of c-KIT or PDGFR is a possible cause in the pathogenesis of SM. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.

Clinical studies in chronic myeloid leukemia

The effectiveness of imatinib is based on overall hematological and cytogenetic response rates and progression-free survival. Except in newly diagnosed 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, uncontrolled Phase II trials were conducted in patients with Philadelphia chromosome-positive (Ph+) CML in advanced, blast, or accelerated-phase disease, other Ph+ leukemias, or chronic-phase CML but who had failed prior interferon-alpha (IFN). A large, open-label, multicenter, international, randomized Phase III study was conducted in patients with newly diagnosed Ph+ CML. In addition, children were 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 imatinib or a combination of interferon-alpha (IFN) plus cytarabine (Ara-C). Patients with no response (no complete hematological response (CHR) at 6 months, increased 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 switch to the alternative treatment arm. In the imatinib 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 1106 patients (553 to each arm) have been randomized. The baseline characteristics are well balanced between the two arms.. Median age was 51 years (range 18–70 years), with 21.9% of patients ≥60 years of age. 59% of patients weremale and 41% female; 89.9% white 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 imatinib and IFN arms, 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, death, loss of CHR or MCyR, or increased WBC in patients who failed to achieve a CHR despite appropriate therapeutic treatment. Major cytogenetic response, hematological response, molecular response (assessment of minimal residual disease), time to accelerated phase or blast crisis, and survival were the main secondary endpoints. Response data are shown in Table 2.

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

(Best response rates)	Imatinib n=553	IFN+Ara-C n=553
Hematological response		
CHR rate *n* (%)	534 (96,6)*	313 (56,6)*
[%95 confidence interval]	94,7, 97,9	52,4, 60,8
Cytogenetic response		
Major response *n* (%)	490 (88,6)*	129 (23,3)*
[%95 confidence interval]	[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 (%)	50,2	9,6
Major response at 24 months (%)	70,2	25
Major response at 84 months (%)	87,9	75

* p<0.001, Fischer' s exact test
** Molecular response percentages are based on available samples

Hematological response criteria (all responses to be confirmed verified ≥4 weeks later):
Number of leucocytes $<10\times10^9$/L, number of platelets $<450\times10^9$/L, myelocyte+metamyelocyte <%5 in blood, no blast cell or promyelocyte in blood, basophile <%20, no extramedullary involvement

Cytogenetic response criteria: Complete (0% Ph+metaphases), partial (l-35%), minor (36-65%) or minimal (66-95%) 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 standardized baseline.

Rates of complete hematological 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 accelerated phase/blast crisis (AP/BC), 31 (5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in white blood cell (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 annual rate of progression to accelerated phase or blast crisis decreased with time on treatment and was less than 1% per year in the fourth and fifth years. The estimated rate of progression-free survival at 84 months was 81.2% in the imatinib group and 60.6% in the control group ($p < 0.001$). Annual progression rates 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). The time to event endpoint is strongly affected by the high rate of transition 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 publication, 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 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 hemorrhages, 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: hematological failure (29%), cytogenetic failure (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥25×10^6 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 hematological response was achieved in 95% of patients.

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

The primary efficacy variable was the rate of hematological response, reported as either complete hematological response, no evidence of leukemia (i.e. clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. A confirmed hematological response was achieved in 71.5% of patients. Importantly, 27.7% of patients also achieved a cytogenetic response, which was complete in 20.4% of patients. For the patients treated at 600 mg, the current estimates for median progression-free-survival and overall survival were 22.9 and 42.5 months, respectively.

Myeloid blast crisis:
260 patients with 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 hematological response, reported as either complete hematological response, no evidence of leukemia, 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 hematological response. The rate of response was also higher in the patients treated at 600 mg as compared to the patients treated at 400 mg (16% vs. 33%, 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 hematological response was 70% with a duration of 2–3 months.

Table 3. Response in 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 (confidence interval of 95%)		
Hematological response[1]	95% (92.3-96.3)	71% (65.3-77.2)	31% (25.2-36.8)
Complete hematological response (CHR)	95%	42%	8%
No evidence of leukemia (NEL)	-	12%	5%
Return to chronic phase (RTC)	-	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]Hematological response criteria (all responses to be confirmed after ≥4 weeks):
CHR: Study 0110 [WBC $<10\times10^9$/L, platelets $<450\times10^9$/L, myelocyte+metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in studies 0102 and 0109 [ANC $\geq1.5\times10^9$/L, platelets $\geq100\times10^9$/L, no blood blasts, BM blasts <5% and no extramedullary disease]
NEL: Same criteria as for CHR but ANC $\geq1\times10^9$/L and platelets $\geq20\times10^9$/L (in studies 0102 and 0109)
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 (in studies 0102 and 0109).
ANC=absolute neutrophil count, BM=bone marrow, PB=peripheral blood, WBC=white blood cell count
[2]Cytogenetic response criteria:
Major response=complete (0% Ph+metaphase) +partial (l-35%) response
[3] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

Pediatric patients:
A total of 26 pediatric patients of age <18 years with either chronic phase CML (n=11) or CML in blast crisis or Ph+acute leukemias (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 imatinib 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 pediatric 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 induces a rapid response in newly diagnosed pediatric 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 imatinib in all subsets of the pediatric population in Philadelphia chromosome (bcr-abl translocation)-positive chronic myeloid leukemia (see section 4.2 for information on pediatric 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 hematological 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 hematological 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 hematological 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 IV, 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/m^2 IV, days 7, 14; IDA 8 mg/m^2 IV (0.5 h), days 7, 8, 14, 15; CP 500 mg/m^2 IV(1 h), day 1; Ara-C 60 mg/m^2 IV, days 22-25, 29-32
Consolidation therapy I, III,V	MTX 500 mg/m^2 IV (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 IV (1 h), days 1-5; VM26 60 mg/m^2 IV (1 h), days 1-5

Study AAU02	
Induction therapy (*de novo*	Daunorubicin 30 mg/m^2 IV, days 1-3, 15-16;

Ph+ALL)	VCR 2 mg total dose IV, days 1, 8, 15, 22; CP 750 mg/m^2 IV, 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 1000 mg/m^2/12 h IV(3 h), days 1-4; Mitoxantrone 10 mg/m^2 IV, 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 IV, days 3-5; MTX 15 mg intrathecal, day 1
Induction therapy I	DEX 10 mg/m^2 oral, days 1-5; VCR 2 mg IV, days 6, 13, 20; Daunorubicin 45 mg/m^2 IV, days 6-7, 13-14
Induction therapy II	CP 1 g/m^2 IV (1 h), days 26, 46; Ara-C 75 mg/m^2 IV (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 IV, day 1; MTX 1.5 g/m^2 IV (24 h), day 1; Etoposide 250 mg/m^2 IV (1 h) days 4-5; Ara-C 2x 2 g/m^2 IV (3 h, q 12 h), day 5

Study AJP01	
Induction therapy	CP 1.2 g/m^2 IV (3 h), day 1; Daunorubicin 60 mg/m^2 IV (1 h), days 1-3; Vincristine 1.3 mg/m^2 IV, 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 IV (24 h), day 1, and Ara-C 2 g/m^2 IV (q 12 h), days 2-3, for 4 cycles
Maintenance	VCR 1.3 g/m^2 IV, day 1; Prednisolone 60 mg/m^2 oral, days 1-5

Study AUS01	
Induction-consolidation therapy	Hyper-CVAD regimen: CP 300 mg/m^2 IV (3 h, q 12 h), days 1-3; Vincristine 2 mg IV, days 4, 11; Doxorubicine 50 mg/m^2 IV (24 h), day 4; DEX 40 mg/day on days 1-4 and 11-14, alternated with MTX 1 g/m^2 IV (24 h), day 1, Ara-C 1 g/m^2 IV (2 h, q 12 h), days 2-3 (total of 8 courses)
Maintenance	VCR 2 mg IV 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; IV: intravenous

Pediatric patients:
In study I2301, a total of 93 pediatric, adolescent and young adult patients (from 18 to 22 years old including 4 patients) with Ph+ALL were enrolled in an open-label, multicentre, 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 1-5, 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.

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 IU/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/m2 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 hematological 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-analyzed to include only those patients age 55 or older.

Clinical studies in SM
One open label, multicentre, phase II clinical trial (study B2225) was conducted testing imatinib in diverse populations of patients suffering from life-threatening diseases associated with ABL, KIT or PDGFR protein tyrosine kinases. SM was diagnosed in 5 of 185 patients treated within this study and 45 of whom had hematological disorders while 140 of whom had diverse solid tumors. SM patients were daily treated with 100 mg and 400 mg imatinib. In 10 published case reports and case series, 25 more SM patients were reported. The age of these patients ranged from 26 to 85 years. These patients were daily administered imatinib in 100 mg to 400 mg doses. Out of overall population treated for SM (30 patients), complete hematological response was obtained from 10 patients (33%) and partial hematological response was obtained from 9 patients (30 %) (overall response rate of 63%). Cytogenetic abnormalities were evaluated in published reports and in 21 of 30 patients treated in study B2225. In eight of these 21 patients, FIP1L1-PDGFRα fusion kinase was detected. Median term of therapy in patients treated within study B2225 was 13 months (interval: 1.4-22.3 months) and the interval in patients responding in published literature ranged from 1 month to a term over 30 months.

Clinical studies in HES/CEL
One open-label, multicentre, phase II clinical trial (study B2225) was conducted testing imatinib 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 imatinib daily. A further 162 patients with HES/CEL, reported in 35 published case reports and case series received imatinib 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-PDGFRαpositive 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 pediatric 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 hematological response, complete cytogenetic response and/or complete molecular response.

Clinical studies in unresectable and/or metastatic GIST
One phase II, open-label, randomized, uncontrolled multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally 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% CI 12-23). Median time to treatment failure in responders was 122 weeks (95% CI 106-147), while in the overall study population it was 84 weeks (95% CI 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 imatinib 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 stabilization 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 imatinib.

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 histological diagnosis of primary GIST expressing Kit protein by immunochemistry and a tumor 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 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.

Imatinib significantly prolonged 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 [0.259-0.610], p<0.0001). At one year the overall RFS was significantly better for imatinib (97.7%) vs. placebo (82.3%), (p<0.0001). 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: tumor size, mitotic index, tumor 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
			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 estimable

A second multicentre, 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: tumor diameter >5 cm and mitotic count >5/50 high power fields (HPF); or tumor diameter >10 cm and any mitotic count or tumor of any size with mitotic count >10/50 HPF or tumors ruptured into the peritoneal cavity. There were a total of 397 patients consented and randomized to the study (199 patients on 12-month arm and 198 patients on 36-month arm), median age was 61 years (range 22 to 84 years). The median time of follow-up was 54 months (from date of randomization to data cut-off), with a total of 83 months between the first patient randomised 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.

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) (Table 8, Figure 1).

In addition, 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).

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 imatinib treatment (SSGXVIII/AIO Trial)

	12-month treatment arm	36-month treatment arm
RFS	%(CI)	%(CI)
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)

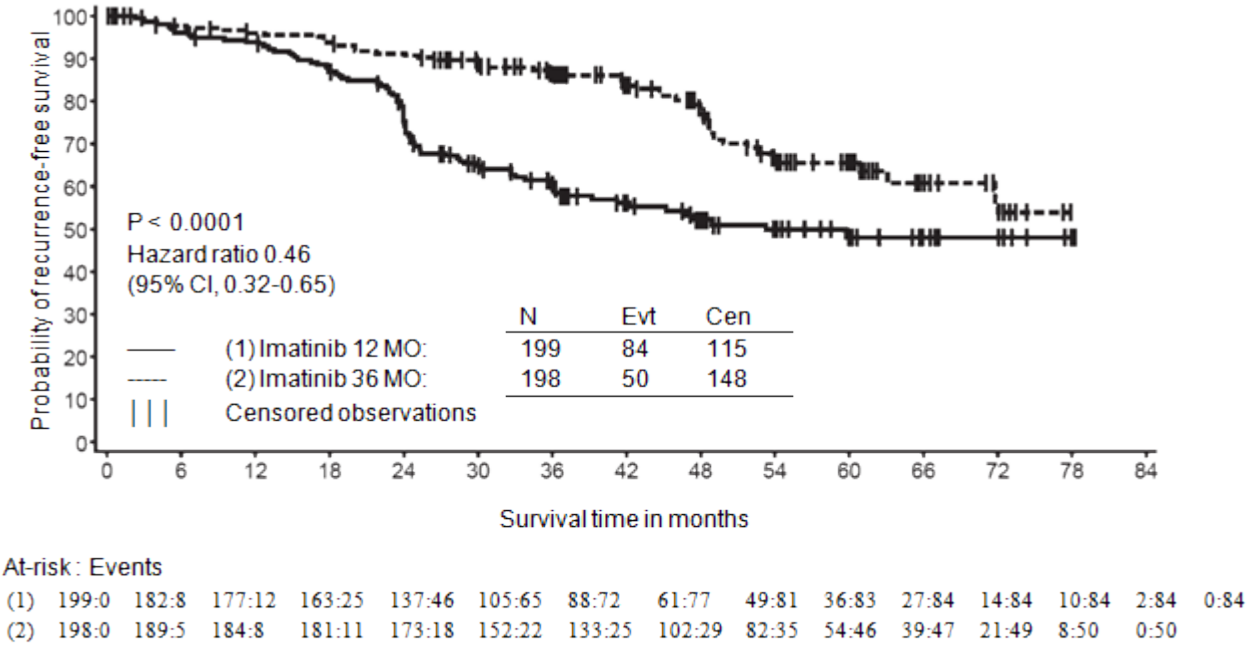
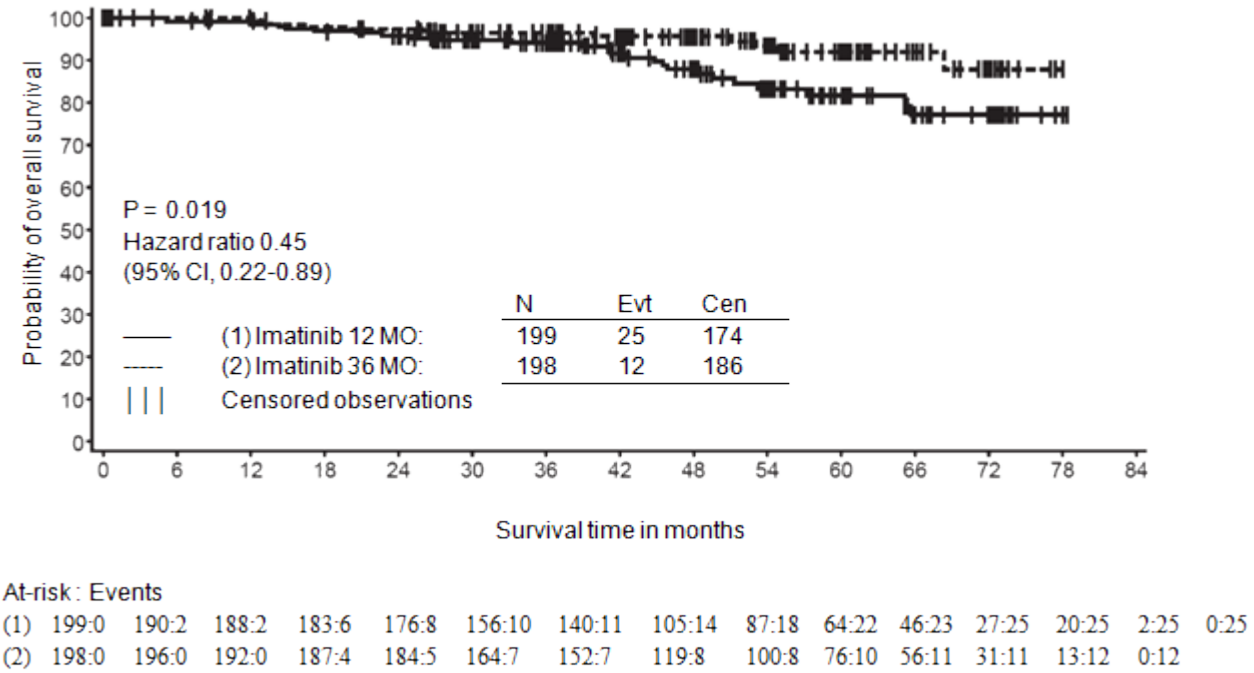


Figure 2. Kaplan-Meier estimates for overall survival (ITT population)



There are no controlled trials in pediatric patients with c-Kit positive GIST. 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 pediatric patients treated for GIST lacked data confirming c-kit or PDGFR mutations which may have led to mixed clinical outcomes.

5.2. Pharmacokinetic properties

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

Absorption:
The average absolute bioavailability of the tablet formulation 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 (CGP71588), which shows similar *in vitro* potency to 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.

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

The *in vitro* results showed that CYP3A4 was the major human P450 enzyme catalyzing 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. Ki 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 (Ki=34.7 µM). This Ki 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:
After an oral ^{14}C-labelled dose of imatinib, approximately 81% of the dose was recovered within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Linearity/Non-linearity:
Following oral administration in healthy volunteers, the t½ 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.

Pharmacokinetic/pharmacodynamic relations
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 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.

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

Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 260 mg/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 alpha acid glycoprotein (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 hematological 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 postimplantation 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 F1 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. F1 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 F1 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 pediatric 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 pediatric exposure at the highest recommended dose of 340 mg/m^2.

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

Colloidal silicon dioxide
Magnesium stearate

Film coating [Opadry II Orange (85F230022)]
Polyvinyl alcohol
Macrogol/PEG 3350
Iron oxide yellow
Talc
Titanium dioxide
Iron oxide red

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
36 months.

6.4. Special precautions for storage
Store at room temperature below 30°C.

6.5. Nature and contents of container
Transparent PVC/Aclar – Alu foil blister packaging
30 tablets are presented with a package leaflet in a cardboard box.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece/ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

241/33

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 12.03.2012
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT

08.09.2021