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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Active substance:
Imatinib 400 mg (as 478 mg imatinib mesylate)
Excipients with known effect:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.
White to off-white, white to cream colored, oblong shaped, biconvex, film-coated tablet.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
IMATIS is indicated for the treatment of:
- Adult and pediatric patients with newly diagnosed Philadelphia chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukemia (CML) for whom bone marrow transplantation is not considered as the first-line of treatment.
- Adult and pediatric patients with chronic phase Ph+ CML after failure of interferon-alpha therapy, or adults and pediatric patients with accelerated phase or blast crisis Ph+ CML.
- Adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα re-arrangement.

The effect of IMATIS on the outcomes of bone marrow transplantation has not been determined.

IMATIS is indicated for:

- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

The adjuvant treatment of adult patients who are at significant risk** based on AFIP* criteria following resection of C-KIT receptor positive GIST (gastrointestinal stromal tumor) or who are with tumor perforation, for three years.

- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and pediatric patients, the effectiveness of imatinib is based on overall hematological and cytogenetic response rates and progression-free survival in CML, on hematological and cytogenetic

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

**Definition of high-risk groups according to AFIP criteria:
1) Tumors located in gastric regions larger than 6 cm and with a mitotic index above 5.
2) Tumors located outside the stomach larger than 10 cm or with a mitotic index above 5.

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, as appropriate.

For doses other than 400 mg and 800 mg (see dosage recommendation below), a 100 mg divisible tablet is available.

For doses of 400 mg or above (see dosage recommendations below), a 400 mg tablet (not divisible) is available.

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

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

Posology for CML in adult patients
The recommended dose of IMATIS for adult patients in chronic-phase CML is 400 mg/day. Chronic-phase CML is defined by meeting all the following criteria: <15% blasts in blood and bone marrow, <20% peripheral blood basophils, and platelet count >100 x 10^9/L.

The recommended dose of IMATIS for adult patients in the accelerated phase is 600 mg/day. The accelerated phase is defined by the presence of any of the following: ≥15% but <30% blasts in blood or bone marrow, ≥30% blasts plus promyelocytes in blood or bone marrow (provided <30% blasts are present), ≥20% peripheral blood basophils, or a platelet count <100 x 10^9/L unrelated to therapy.

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

Duration of treatment: In clinical studies, imatinib treatment was continued until disease progression. The effect of discontinuing therapy after achieving a complete cytogenetic response has not been

investigated.

In the absence of serious adverse drug reactions and serious neutropenia or thrombocytopenia not related to leukemia, dose increases may be considered in the following situations: for patients with chronic phase disease, from 400 mg to 600 mg or 800 mg, or for patients with accelerated phase or blast crisis, from 600 mg to a maximum of 800 mg (administered as 400 mg twice daily): disease progression (at any time); failure to achieve a satisfactory hematologic 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 hematologic and/or cytogenetic response. Given the potential for an increased incidence of adverse reactions at higher doses, patients should be closely monitored after dose escalation.

Pediatric Posology for CML
Dosage adjustment for children should be based on body surface area (mg/m²). A daily dose of 340 mg/m² is recommended for children with chronic phase CML and advanced phase CML (the total dose should not exceed 800 mg). Treatment can be administered once daily, or alternatively, the daily dose can be divided into two administrations, one in the morning and one in the evening. The dosage recommendation is currently based on a limited number of pediatric patients (see sections 5.1 and 5.2). There is no experience regarding the treatment of children under the age of 2.

In the absence of serious adverse drug reactions and serious neutropenia or thrombocytopenia not related to leukemia, dose increases may be considered in the following situations for children: from 340 mg/m² to 570 mg/m² daily (without exceeding the total dose of 800 mg): disease progression (at any time); failure to achieve a satisfactory hematologic 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 hematologic and/or cytogenetic response. Given the potential for an increased incidence of adverse reactions at higher doses, patients should be closely monitored after dose escalation.

Posology for Adult Patients with Ph+ ALL
The recommended dose of IMATIS for adult patients with Ph+ ALL is 600 mg/day. In the management of this disease, expert hematologists should monitor the treatment at all stages.
Treatment Scheme: Based on current data, when used in combination with chemotherapy during the induction, consolidation, and maintenance phases of chemotherapy, a daily dose of 600 mg has been proven to be effective and safe for newly diagnosed adult patients with Ph+ ALL (see section 5.1). The duration of imatinib treatment may vary depending on the selected treatment regimen, but longer exposure to imatinib has generally yielded better results.

For relapsed or resistant Ph+ ALL in adult patients, 600 mg/day of IMATIS monotherapy is safe, effective, and may be continued until disease progression occurs.

Posology for Children with Ph+ ALL
Dosage adjustment for children should be based on body surface area (mg/m²). A daily dose of 340 mg/m² is recommended for children with Ph+ ALL (the total dose should not exceed 600 mg).

Posology for MDS/MPD
The recommended dose of IMATIS for adult patients with MDS/MPD is 400 mg/day.
Treatment Duration: In the only clinical study conducted so far, imatinib treatment was continued until disease progression (see section 5.1). During the analysis, the median treatment duration was 47 months (range: 24 days - 60 months).

Posology for HES/CEL
The recommended dose of IMATIS for adult patients with HES/CEL is 100 mg/day.
If evaluations show an inadequate response to treatment, the dose may be increased from 100 mg to 400 mg in the absence of adverse drug reactions.
Treatment should be continued as long as the patient benefits from it.

Posology for GIST
For adults with unresectable and/or metastatic malignant GIST, the recommended dose of IMATIS is 400 mg/day.

There are limited data regarding the effects of dose escalation from 400 mg to 600 mg or 800 mg in patients who progress on lower doses (see section 5.1).

Treatment Duration: In clinical trials conducted with GIST patients, imatinib treatment was continued until disease progression. During the analysis, the median treatment duration was 7 months (range: 7 days to 13 months). The effect of stopping treatment after achieving a response has not been studied.

For adult patients receiving adjuvant treatment following GIST resection, the recommended dose of IMATIS is 400 mg/day. The optimal treatment duration has not yet been determined. In the clinical study supporting this indication, the treatment duration was 36 months (see section 5.1).

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

Dosage Adjustment for Adverse Reactions
Non-Hematologic Adverse Reactions
If a serious non-hematologic adverse reaction occurs during IMATIS use, treatment should be interrupted until the event resolves. Afterwards, treatment may be resumed appropriately depending on the initial severity of the event.

If bilirubin levels rise > 3 x the upper limit of normal (ULN) or liver transaminases rise > 5 x ULN, IMATIS should be discontinued until bilirubin levels return to < 1.5 x ULN and transaminase levels return to < 2.5 x ULN. Subsequently, treatment with IMATIS may be resumed at a reduced daily dose. For adults, the dose should be reduced from 400 mg to 300 mg, from 600 mg to 400 mg, or from 800 mg to 600 mg, and for children, from 340 mg/m²/day to 260 mg/m²/day.

Hematologic Adverse Reactions
For serious neutropenia and thrombocytopenia, dose reduction or treatment interruption should be considered as outlined in the table below.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

HES/CEL (starting dose 100 mg)	ANC<$1x10^9$/L and/or platelets<$50x10^9$/L	1. Stop IMATIS until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMATIS at the previous dose (i.e., before the serious adverse reaction).
Chronic phase CML, MDS/MPD, and GIST (starting dose 400 mg) HES/CEL (400 mg dose)	ANC<$1x10^9$/L and/or platelets<$50x10^9$/L	1. Stop IMATIS until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMATIS at the previous dose

		(i.e., before the serious adverse reaction). 3. If ANC < 1 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and continue IMATIS at a reduced dose of 300 mg.
Pediatric chronic phase CML (340 mg/m² dose)	ANC<1x10^9/L and/or platelets<50x10^9/L	1. Stop IMATIS until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMATIS at the previous dose (i.e., before the serious adverse reaction). 3. If ANC < 1 x 10^9/L and/or platelets < 50 x 10^9/L recur, repeat step 1 and continue IMATIS at a reduced dose of 260 mg/m².
Accelerated phase CML, blast crisis, and Ph+ ALL (starting dose 600 mg)	[a]ANC<0.5x10^9/L and/or platelets<10x10^9/L	1. Check if the cytopenia is related to leukemia (bone marrow aspiration or biopsy). 2. If cytopenia is not related to leukemia, reduce IMATIS dose to 400 mg. 3. If cytopenia persists for 2 weeks, reduce the dose to 300 mg. 4. If cytopenia persists for 4 weeks and is still not related to leukemia, stop IMATIS until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L, then continue treatment at 300 mg.
Pediatric accelerated phase CML and blast crisis (starting dose 340 mg/m²)	[a]ANC<0.5x10^9/L and/or platelets<10x10^9/L	1. Check if the cytopenia is related to leukemia (bone marrow aspiration or biopsy). 2. If cytopenia is not related to leukemia, reduce IMATIS dose to 260 mg/m². 3. If cytopenia persists for 2 weeks, reduce the dose to 200 mg/m². 4. If cytopenia persists for 4 weeks and is still not related to leukemia, stop IMATIS until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L, then continue treatment at 200 mg/m².
DFSP (800 mg dose)	ANC<1x10^9/L and/or platelets<50x10^9/L	1. Stop IMATIS until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Continue treatment with IMATIS at the 600 mg dose. 3. If ANC < 1 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and continue IMATIS at a reduced dose of 400 mg.
ANC = absolute neutrophil count [a]occurring after at least 1 month of treatment		

Additional Information for Special Populations:

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, and 5.2).

Table 2: Liver Dysfunction Classification

Liver Dysfunction	Liver Function Tests

Mild	Total bilirubin = 1.5 × ULN, AST: >ULN (can be normal or <ULN if total bilirubin >ULN)
Moderate	Total bilirubin: >1.5-3 × ULN, AST: any
Severe	Total bilirubin: >3-10 × ULN, AST: any

ULN = Upper Limit of Normal
AST = Aspartate Aminotransferase

Renal insufficiency
Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see sections 4.4 and 5.2).

Pediatric population
There is no experience in children with CML below 2 years of age and with Ph+ALL below 1 year of age (see section5.1). There is very limited experience in children with MDS/MPD, DFSP, GIST and HES/CEL.

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

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

4.3. Contraindications
Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4. Special warnings and precautions for use
IMATIS has the potential for drug interactions when used in combination with other medications. Caution should be exercised when IMATIS is administered 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, dihydroergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine), or warfarin and other coumarin derivatives (see section 4.5).

The concomitant use of imatinib with CYP3A4 enzyme inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, or *Hypericum perforatum* [St. John's Wort]) may significantly reduce imatinib exposure and increase the risk of therapeutic failure. Therefore, the concurrent use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).

Hypothyroidism:
Cases of clinical hypothyroidism have been reported in patients who have undergone thyroidectomy and are receiving levothyroxine replacement therapy during imatinib treatment (see section 4.5). In such patients, thyroid-stimulating hormone (TSH) levels should be closely monitored.

Hepatotoxicity:
Imatinib is primarily metabolized in the liver, and only 13% of its excretion occurs via the kidneys. In patients with liver dysfunction (mild, moderate, and severe), peripheral blood counts and liver enzymes should be closely monitored (see sections 4.2, 4.8, 5.1, and 5.2). In GIST patients, liver metastases that may lead to liver failure are likely to be observed.

Cases of liver damage, including liver failure and hepatic necrosis, have been reported with imatinib. When imatinib is combined with high-dose chemotherapy regimens, an increase in serious hepatic reactions has been reported. In cases where imatinib is combined with chemotherapy regimens known to be associated with liver dysfunction, liver function should be carefully monitored (see sections 4.5 and 4.8).

Fluid Retention:
Serious fluid retention (pleural effusion, edema, pulmonary edema, ascites, superficial edema) has been reported in approximately 2.5% of newly diagnosed CML patients receiving imatinib. Therefore, regular weight monitoring is recommended. Unexpected, rapid weight gain should be thoroughly investigated, and if necessary, appropriate supportive treatment should be administered, and therapeutic measures should be taken. In clinical studies, the incidence of these events was found to be higher in elderly patients and those with a history of cardiac disease. Therefore, caution is advised in patients with cardiac dysfunction.

Patients with Heart Disease:
Patients with heart disease, those at risk of heart failure, or with a history of renal failure should be carefully monitored, and any symptoms suggesting heart or kidney failure should be evaluated and treated accordingly.

In patients with occult infiltration of the myocardium by hypereosinophilic syndrome (HES) cells, cases of isolated cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon initiation of imatinib therapy. It has been reported that this condition may be reversible with the use of systemic steroids, supportive circulatory measures, and temporary discontinuation of imatinib treatment. Since rare cardiac side effects have been reported with imatinib, a careful benefit/risk assessment should be made before initiating IMATIS therapy in the HES/CEL (chronic eosinophilic leukemia) population.

PDGFR gene rearrangements may be associated with myelodysplastic/myeloproliferative diseases (MDS/MPD) and systemic mastocytosis, which are related to high eosinophil levels. Therefore, in patients with MDS/MPD, systemic mastocytosis (SM), and HES/CEL, imatinib should only be administered after evaluation by a cardiology specialist, including echocardiographic examination and measurement of serum troponin levels. If any abnormalities are detected, the patient should be monitored in collaboration with a cardiology specialist, and systemic steroids (1-2 mg/kg) may be considered for 1-2 weeks along with imatinib therapy at the beginning.

Gastrointestinal Bleeding:
A study conducted in patients with unresectable and/or metastatic GIST has reported both gastrointestinal and intra-tumoral hemorrhages (see section 4.8). Based on the available data, no specific predisposing factors that put GIST patients at higher risk for both types of bleeding (e.g., tumor size, tumor location, coagulation disorders) have been identified. Since increased vascularity and susceptibility to bleeding are part of the nature of GIST and the clinical course of the disease, standard procedures and protocols for bleeding monitoring and management should be applied in all

patients.

In addition, post-marketing experience has reported rare cases of gastrointestinal hemorrhage due to gastric antral vascular ectasia (GAVE) in patients with CML, ALL, and other diseases (see section 4.8). If necessary, discontinuation of IMATIS therapy should be considered.

Tumor Lysis Syndrome (TLS):
Due to the possibility of tumor lysis syndrome (TLS), it is recommended that clinically significant dehydration be corrected and elevated uric acid levels treated before starting IMATIS (see section 4.8).

Hepatitis B Reactivation:
Hepatitis B virus (HBV) reactivation has occurred in patients who are chronic carriers of HBV and are treated with BCR-ABL tyrosine kinase inhibitors. Some cases have resulted in acute liver failure or fulminant hepatitis, which may require liver transplantation or lead to death.

Before starting IMATIS therapy, patients should be tested for HBV infection. Patients with positive HBV serology (including those with active disease) and those who test positive for HBV infection during treatment should be consulted with liver disease and HBV treatment specialists before starting therapy. HBV carriers who require IMATIS treatment should be closely monitored for signs and symptoms of active HBV infection during and for several months after discontinuing therapy (see section 4.8).

Phototoxicity:
Due to the risk of phototoxicity associated with IMATIS therapy, exposure to direct sunlight should be avoided or minimized. Patients should be advised to take precautions such as wearing protective clothing or using sunscreens with a high sun protection factor (SPF).

Thrombotic Microangiopathy:
BCR-ABL tyrosine kinase inhibitors (TKIs), including individual case reports for imatinib, have been associated with thrombotic microangiopathy (TMA) (see section 4.8). If laboratory or clinical findings related to TMA occur in a patient receiving IMATIS, treatment should be discontinued, and a comprehensive evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13 antibody determination, should be performed. If there is low ADAMTS13 activity with elevated anti-ADAMTS13 antibodies, IMATIS therapy should not be restarted.

Laboratory Tests:
Regular complete blood counts should be performed during IMATIS therapy. In CML patients, treatment with imatinib has been associated with neutropenia or thrombocytopenia. However, the onset of these cytopenias depends on the stage of the disease being treated, and they occur more frequently in patients with accelerated phase CML or blast crisis compared to those with chronic phase CML. In this case, IMATIS therapy may be discontinued or the dose reduced as suggested in Section 4.2.

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

In patients with impaired renal function, plasma exposure to imatinib is higher compared to patients with normal renal function; this is likely due to higher plasma levels of alpha-acid glycoprotein (AGP), a protein that binds to imatinib. In patients with renal impairment, the lowest starting dose

should be given. Patients with severe renal impairment should be treated with caution. The dose may be reduced if not tolerated (see sections 4.2 and 5.2).

Long-term treatment with imatinib may be associated with clinically significant reduction in renal function. Therefore, renal function should be assessed before starting imatinib therapy and closely monitored during treatment, with particular attention given to patients showing risk factors for renal dysfunction. If renal dysfunction occurs, appropriate management and treatment should be prescribed according to standard treatment guidelines.

Pediatric Population
Case reports of growth retardation in children and prepubertal adolescents receiving imatinib have been reported. An observational study in the pediatric population with CML found a statistically significant (but clinically uncertain) reduction in median height standard deviation scores in two small subgroups at 12 and 24 months, regardless of pubertal status or gender. Growth should be closely monitored in children receiving imatinib therapy (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction
Drugs that may increase imatinib plasma concentrations:
Substances that inhibit CYP3A4 activity (e.g., protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, and boceprevir; azole antifungal agents such as ketoconazole, itraconazole, posaconazole, and voriconazole; certain macrolides such as erythromycin, clarithromycin, and telithromycin) may reduce metabolism and increase imatinib concentrations. In healthy volunteers, co-administration of a single dose of ketoconazole (a CYP3A4 inhibitor) resulted in a significant increase in imatinib exposure (mean C_{max} and AUC increased by 26% and 40%, respectively). IMATIS should be used with caution when given with CYP3A4 inhibitors.

Drugs that may decrease imatinib plasma concentrations:
Substances that induce CYP3A4 activity (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone, or St. John's Wort, also known as Hypericum perforatum) may significantly reduce exposure to IMATIS and potentially increase the risk of treatment failure. After multiple 600 mg doses of rifampicin were administered prior to a single 400 mg dose of imatinib, C_{max} and $AUC_{(0-\infty)}$ values decreased by at least 54% and 74%, respectively, compared to values in the absence of rifampicin treatment. Similar results were observed in patients with malignant glioma receiving enzyme-inducing antiepileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, and phenytoin. Plasma AUC for imatinib was reduced by 73% in patients using EIAEDs compared to those not using them. Co-administration of rifampicin or other strong CYP3A4 inducers with imatinib should be avoided.

Drugs whose plasma concentration may be altered by imatinib:
Imatinib increases the mean C_{max} and AUC of simvastatin (a CYP3A4 substrate) by 2-fold and 3.5-fold, respectively, indicating that CYP3A4 is inhibited by imatinib. Therefore, IMATIS should be used with caution when co-administered with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, dihydroergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine). IMATIS may increase the plasma concentrations of other drugs metabolized by CYP3A4 (e.g., triazolobenzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, such as statins, etc.).

Due to the known increased risk of bleeding with imatinib (e.g., hemorrhage), patients requiring

anticoagulation should be treated with low molecular weight or standard heparin instead of coumarin derivatives such as warfarin.

In vitro, imatinib inhibits the activity of the cytochrome P450 isoenzyme CYP2D6 at similar concentrations affecting CYP3A4 activity. Imatinib administered at a dose of 400 mg twice daily has an inhibitory effect on CYP2D6-mediated metabolism of metoprolol; C_{max} and AUC values for metoprolol increase by approximately 23% (90% CI [1.16–1.3]). When co-administered with CYP2D6 substrates, imatinib does not require dose adjustments, but caution is advised when using CYP2D6 substrates with a narrow therapeutic window, such as metoprolol. Clinical monitoring is recommended for patients treated with metoprolol.

Imatinib inhibits paracetamol O-glucuronidation with a Ki value of 58.5 mcgmol/L *in vitro*. However, this inhibition was not observed *in vivo* after administration of 400 mg imatinib and 1000 mg paracetamol. Higher doses of imatinib and paracetamol have not been studied. Therefore, caution is advised when using high doses of IMATIS and paracetamol together.

In patients who have undergone thyroidectomy and are using levothyroxine, co-administration of IMATIS may decrease plasma exposure to levothyroxine (see section 4.4). Caution is advised, although the mechanism of this interaction is still not known.

There is clinical experience with the use of imatinib in combination with chemotherapy in patients with Ph+ ALL (see section 5.1), but drug-drug interactions between imatinib and chemotherapy regimens have not been well-defined. Adverse effects of imatinib, such as hepatotoxicity, myelosuppression, and others, may be increased, and concomitant use with L-asparaginase has been reported to be associated with increased hepatotoxicity (see section 4.8). Therefore, the combination use of IMATIS requires special attention.

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 principles
Pregnancy category is “D”.

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should be advised to use effective contraception during treatment and for at least 15 days after treatment discontinuation.

Pregnancy
There is limited data on the use of imatinib in pregnant women. Post-marketing reports have shown spontaneous abortions and congenital anomalies in infants of women taking imatinib. However, animal studies have shown reproductive toxicity (see section 5.3), and the potential risk to the fetus is unknown. IMATIS should not be used during pregnancy unless absolutely necessary. If used during pregnancy, the patient should be informed of the potential risks to the fetus.

Lactation
There is limited information on the transfer of imatinib into human breast milk. Studies in two

breastfeeding women have shown that both imatinib and its active metabolite may pass into breast milk. The milk-to-plasma ratio observed in one patient was 0.5 for imatinib and 0.9 for the metabolite, suggesting that the metabolite passes into the milk to a greater extent. Considering the total concentration of imatinib and its metabolite and the maximum daily milk intake of infants, total exposure is expected to be low (about 10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, mothers should avoid breastfeeding during IMATIS treatment and for at least 15 days after treatment discontinuation.

Fertility
In preclinical studies, although effects on reproductive parameters were observed, fertility was not affected in female and male mice (see section 5.3). No studies have been conducted on the effects of imatinib on fertility and gametogenesis in patients. Patients undergoing IMATIS treatment who are concerned about fertility should consult their doctor.

4.7. Effects on ability to drive and use machines
Patients should be advised that they might experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

4.8. Undesirable effects
In patients with advanced malignancies, numerous complicating medical conditions may make it difficult to assess the causality of adverse reactions due to the underlying disease, progression, and the simultaneous use of multiple medical products.

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

With two exceptions, adverse reactions were similar across all indications. Compared to GIST, more myelosuppression was observed in CML patients, which is likely related to the underlying disease. In a study of patients with unresectable and/or metastatic GIST, 7 (5%) patients experienced CTC grade 3/4 GI bleeding (3 patients), tumor-related bleeding (3 patients), or both (1 patient). GI tumor regions may have been the source of the GI bleeding (see section 4.4). GI and tumor-related bleeding can be severe and sometimes fatal. The most frequently reported drug-related adverse reactions (≥10%) in both indications were mild nausea, vomiting, diarrhea, abdominal pain, fatigue, muscle pain, muscle cramps, and rash. Superficial edema was a common finding across all studies, typically described as periorbital or lower limb edema. However, these edemas were rarely severe and could be controlled with diuretics, other supportive measures, or by reducing the imatinib dose.

When imatinib was combined with high-dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of elevated transaminases and hyperbilirubinemia was observed. Considering the limited safety database, the adverse events reported in children so far are consistent with the known safety profile in adult Ph+ ALL patients. Although the safety database in pediatric Ph+ ALL patients is very limited, no new safety concerns have been identified.

Various adverse reactions, such as pleural effusion, ascites, pulmonary edema, and superficial edema, with or without rapid weight gain, can collectively be described as "fluid retention." These reactions can typically be controlled by temporarily discontinuing imatinib treatment and using diuretics or

other appropriate supportive care measures.

On the other hand, some of these reactions can be severe or life threatening, and several patients in blast crisis have died due to a complex clinical history involving pleural effusion, congestive heart failure, and renal failure. No specific safety findings were observed in pediatric clinical trials.

Adverse reactions reported as more than an isolated case are listed below according to organ system class and frequency. The frequency categories are defined using the following standard: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from available data).
Adverse effects are presented in frequency order, with the most frequent listed first within each frequency group.
Adverse reactions and their frequencies are summarized in Table 3.

Table 3: Summary of Adverse Reactions in Table Format

Infections and Infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia, sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Unknown:	Hepatitis B reactivation*
Benign, Malignant, and Unspecified Neoplasms (including cysts and polyps)	
Rare:	Tumor lysis syndrome
Unknown	Tumor bleeding/tumor necrosis*
Immune System Disorders	
Unknown:	Anaphylactic shock*
Blood and Lymphatic System Disorders	
Very Common:	Neutropenia, thrombocytopenia, anemia
Common:	Pancytopenia, febrile neutropenia
Uncommon:	Thrombocytosis, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare:	Hemolytic anemia, thrombotic microangiopathy
Metabolism and Nutrition Disorders	
Common:	Anorexia

Uncommon:	Hypokalemia, increased appetite, hypophosphatemia, decreased appetite, dehydration, gout, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia
Rare:	Hyperkalemia, hypomagnesemia
Psychiatric Disorders	
Common:	Insomnia
Uncommon:	Depression, decreased libido, anxiety
Rare:	Confusion
Nervous System Disorders	
Very Common:	Headache[2]
Common:	Dizziness, vertigo, paresthesia, taste disturbances, hypoesthesia
Uncommon:	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, brain hemorrhage
Rare:	Increased intracranial pressure, convulsion, optic neuritis
Unknown:	Cerebral edema*
Eye Disorders	
Common:	Eyelid edema, increased lacrimation, conjunctival hemorrhage, conjunctivitis, dry eyes, blurred vision
Uncommon:	Eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema
Rare:	Cataract, glaucoma, papilledema
Unknown:	Vitreal Hemorrhage*
Ear and Inner Ear Disorders	
Uncommon:	Vertigo, tinnitus, hearing loss
Cardiac Disorders	
Uncommon:	Palpitations, tachycardia, congestive heart failure, pulmonary edema

Rare:	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Unknown:	Pericarditis*, cardiac tamponade*
Vascular Disorders[4]	
Common:	Orthostatic hypotension, bleeding
Uncommon:	Hypertension, hematoma, subdural hematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Unknown:	Thrombosis/embolism*
Respiratory, Chest, and Mediastinal Disorders	
Common:	Dyspnea, nosebleeds, cough
Uncommon:	Pleural effusion, pharyngolaryngeal pain, pharyngitis
Rare:	Pleural pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage
Unknown:	Acute respiratory failure*, interstitial lung disease*
Gastrointestinal Disorders	
Very Common:	Nausea, diarrhea, vomiting, dyspepsia, abdominal pain
Common:	Excessive intestinal gas, bloating, gastroesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal bleeding, belching, melena, esophagitis, ascites, gastric ulcer, hematemesis, lip inflammation, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Unknown:	Ileus/intestinal obstruction*, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (GAVE)*
Hepato-biliary Disorders	
Common:	Increase in liver enzymes
Uncommon:	Hyperbilirubinemia, hepatitis, jaundice
Rare:	Liver failure[8], hepatic necrosis
Skin and Subcutaneous Tissue Disorders	

Very Common:	Periorbital edema, dermatitis/eczema/skin rash
Common:	Itching, facial edema, skin dryness, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Pustular rash, contusion, increased sweating, urticaria, ecchymosis, increased tendency to bruising, hypotrichosis, hypopigmentation of the skin, exfoliative dermatitis, nail breakage, folliculitis, petechiae, psoriasis, purpura, hyperpigmentation of the skin, bullous eruptions, panniculitis[12]
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail color loss, angioneurotic edema, vesicular rash, erythema multiforme, leukocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), pemphigus*
Unknown:	Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)*, lichenoid keratosis*, lichen planus*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS syndrome)*, pseudoporphyria
Musculoskeletal and Connective Tissue Disorders	
Very Common:	Muscle spasms and cramps, myalgia including musculoskeletal pain[9], arthralgia, bone pain[10]
Common:	Joint swelling
Uncommon:	Muscle and joint stiffness, osteonecrosis*
Rare:	Muscle weakness, arthritis, rhabdomyolysis/myopathy
Unknown:	Growth retardation in children*
Kidney and Urinary Tract Disorders	
Uncommon:	Kidney pain, hematuria, acute renal failure, increased frequency of urination
Unknown:	Chronic kidney failure
Reproductive System and Breast Disorders	
Uncommon:	Gynecomastia, erectile dysfunction, menorrhagia, irregular menstruation, sexual dysfunction, nipple pain, breast enlargement, scrotal edema
Very Rare:	Hemorrhagic corpus luteum/hemorrhagic ovarian cyst
General Disorders and Application Site Conditions	

Very Common:	Fluid retention and edema, fatigue
Common:	Weakness, fever, anasarca, shivering episodes, muscle stiffness
Uncommon:	Chest pain, malaise
Laboratory Findings	
Very Common:	Weight gain
Common:	Weight loss
Uncommon:	Elevated serum creatinine levels, elevated creatine phosphokinase levels, elevated lactate dehydrogenase levels, elevated alkaline phosphatase levels
Rare:	Elevated serum amylase levels

*These types of reactions have mainly been reported from post-marketing experience with imatinib. These data include serious adverse events from ongoing studies, spontaneous case reports, expanded access programs, clinical pharmacology studies, and exploratory studies for unapproved indications. Since these reactions have been reported from a population of uncertain size, it is not always possible to reliably predict their frequency or establish a causal relationship with imatinib exposure.
[1]Pneumonia has been most frequently reported in transformed CML patients and GIST patients.
[2]Headache has been most frequently observed in GIST patients.
[3]Cardiac events, including congestive heart failure, have been observed more frequently in transformed CML patients than in chronic CML patients on a per patient-year basis.
[4]Flushing has been most frequently observed in GIST patients; bleeding (hematoma, hemorrhage) is the most common occurrence in GIST and transformed CML (CML-AF and CML-BK) patients.
[5]Pleural effusion has been reported more commonly in GIST patients and transformed CML (CML-AF and CML-BK) patients than in chronic CML patients.
[6+7] Abdominal pain and gastrointestinal bleeding have been most frequently observed in GIST patients.
[8] Some fatal cases of hepatic failure and hepatic necrosis have been reported.
[9] Musculoskeletal pain has been observed during or after discontinuation of imatinib treatment in post-marketing experiences.
[10] Musculoskeletal pain and related events have been observed more frequently in CML patients than in GIST patients.
[11] Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia, and other serious coexisting conditions.
[12] Including erythema nodosum.

Laboratory Test Abnormalities

Hematology

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies and are thought to occur more frequently at higher doses, such as ≥750 mg (Phase I study). However, the occurrence of cytopenias has also clearly depended on the stage of the disease. The frequency of grade 3 or 4 neutropenia (ANC $<1x10^9$/L) and thrombocytopenia (platelet count

<50x10^9/L) was found to be 4 to 6 times higher in blast crisis and accelerated phase compared to newly diagnosed chronic phase CML patients (16.7% for neutropenia and 8.9% for thrombocytopenia). In newly diagnosed chronic phase CML cases, grade 4 neutropenia (ANC <0.5x10^9/L) and thrombocytopenia (platelet count <10x10^9/L) were observed at rates of only 3.6% and <1%, respectively. The median duration of neutropenic and thrombocytopenic episodes generally occurred between weeks 2 and 3 and between weeks 3 and 4, respectively. These events can typically be managed by reducing the dose of IMATIS or interrupting treatment. However, in some rare cases, they may lead to the permanent discontinuation of treatment. In pediatric CML patients, the most commonly observed toxicities have been grade 3 or 4 cytopenias, including neutropenia, thrombocytopenia, and anemia. These events generally occur within the first few months of treatment.

In a study involving patients with unresectable and/or metastatic GIST, grade 3 and 4 anemia was reported in 5.4% and 0.7% of patients, respectively, which could be associated with gastrointestinal or intratumoral bleeding in some cases. Grade 3 and 4 neutropenia were observed in 7.5% and 2.7% of patients, respectively, and grade 3 thrombocytopenia in 0.7% of patients. No cases of grade 4 thrombocytopenia were reported. Reductions in white blood cell (WBC) and neutrophil counts were noted, particularly during the first six weeks of treatment, and subsequently stabilized.

Biochemistry
In CML patients, severe increases in transaminases (<5%) or bilirubin (<1%) were reported and were generally managed by dose reduction or discontinuation (median duration of these episodes was approximately one week). Less than 1% of CML patients permanently discontinued treatment due to liver laboratory abnormalities. In GIST patients (study B2222), grade 3 or 4 elevations in ALT (alanine aminotransferase) occurred in 6.8% of cases, and grade 3 or 4 elevations in AST (aspartate aminotransferase) in 4.8% of cases. Bilirubin elevation was observed in less than 3% of cases.

Cases of cytolytic and cholestatic hepatitis and liver failure have been reported, some resulting in death, including a case involving a patient who used high doses of paracetamol.

Description of selected adverse reactions
Hepatitis B Reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases have resulted in acute liver failure or fulminant hepatitis, leading to liver transplantation or death (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 the 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. In the event of overdose, the patient should be observed and appropriate symptomatic treatment given. Generally, the reported outcome in these cases was “improved” or “recovered”. Events that have been reported at different dose ranges are as follows:

Adult population
1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, 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 creatine phosphokinase, increased bilirubin, and 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, and increased transaminases.

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

Pediatric population
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 experienced decreased white blood cell count and diarrhea.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

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

Pharmacodynamic effects
Imatinib is a protein tyrosine kinase inhibitor that strongly inhibits BCR-ABL tyrosine kinase in vitro, at the cellular level, and in vivo. The compound selectively inhibits proliferation and induces apoptosis in fresh leukemic cells from patients with Philadelphia chromosome-positive CML and acute lymphoblastic leukemia (ALL), as well as in BCR-ABL-positive cell lines.

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

Imatinib also inhibits the receptors for platelet-derived growth factor (PDGF-R) and stem cell factor (SCF), the receptor tyrosine kinase c-KIT, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in GIST cells expressing an activating KIT mutation. Structural activation resulting from the fusion of PDGF receptors or Abl protein tyrosine kinases with various partner proteins or from the abnormal production of PDGF has been implicated in the pathogenesis of MDS/MPD, HES/CEL, and DFSP. Additionally, constitutive activation of c-KIT or PDGFR is a probable cause of SM pathogenesis. Imatinib inhibits signaling and cell proliferation driven by dysregulated PDGFR or Abl kinase activity.

Clinical Studies in Chronic Myeloid Leukemia
The efficacy of imatinib is based on the hematological and cytogenetic response rates and disease-free survival times obtained as a whole. Apart from newly diagnosed chronic-phase CML, there is no controlled study demonstrating clinical benefits such as improvement in disease-related symptoms or increased survival time.

Three large, international, open-label, uncontrolled Phase II studies were conducted in patients with Philadelphia chromosome-positive (Ph+) CML in advanced, blast, or accelerated-phase disease, in other Ph+ leukemias, or in chronic-phase CML patients who had previously failed interferon-alpha (IFN) treatment. A large, open-label, multicenter, international, randomized Phase III study was conducted in newly diagnosed Ph+ CML patients. Additionally, children were treated in two Phase I studies and one Phase II study.

In all clinical studies, 38-40% of the patients were ≥60 years old, and 10-12% were ≥70 years old.

Chronic phase, newly diagnosed: In this Phase III study conducted in adult patients, treatment with single-agent imatinib was compared to treatment with interferon-alpha (IFN) plus cytarabine (Ara-C) combination. Patients who showed non-responsiveness (lack of complete hematological response (CHR) at 6 months, increasing WBC, or lack of major cytogenetic response (MCR) at 24 months), loss of response (loss of CHR or MCR), or severe intolerance to treatment were allowed to switch to the alternative treatment arm. Patients in the imatinib arm were treated with a daily dose of 400 mg. In the IFN group, patients were treated with a target dose of 5 MIU/m²/day IFN subcutaneously in combination with Ara-C 20 mg/m²/day subcutaneously for 10 days/month.

A total of 1106 patients (553 in each group) were randomized. Baseline characteristics between the two arms were well balanced. The median age was 51 years (range 18-70 years), and 21.9% of the patients were 60 years or older. The cohort consisted of 59% males and 41% females, with 89.9% white and 4.7% black patients. Seven years after the inclusion of the last patient in the study, the median duration of first-line treatment was 82 months in the imatinib arm and 8 months in the IFN arm. The median duration of second-line treatment with imatinib was 64 months. Overall, the average daily dose administered to patients receiving first-line imatinib was 406±76 mg. The primary efficacy endpoint of the study was progression-free survival. Progression was defined as any of the following events: progression to accelerated phase or blast crisis, death, loss of CHR or MCR, or an increase in WBC in patients who failed to achieve a CHR despite appropriate therapeutic treatment. Secondary key endpoints included major cytogenetic response, hematological response, molecular response (assessment of minimal residual disease), time to progression to accelerated phase or blast crisis, and overall survival. Response data are shown in Table 4.

Table 4: Responses in the newly diagnosed CML study (84 months of data)

	Imatinib	**IFN+Ara-C**
(Best Response Rates)	n=553	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 (%)	153/305=%50.2	8/83=%9.6
Major Response at 24 months (%)	73/104=%70.2	3/12=%25
Major Response at 84 months (%)	102/116=%87.9	3/4=%75

* p<0,001, Fischer's exact test
**Molecular response rates depend on accessible samples.
Criteria for Hematological Response (All responses must be confirmed after ≥4 weeks):
The WBC count in the blood is < 10 x 10^9/L, platelet count < 450 x 10^9/L, myelocytes + metamyelocytes < 5%; there are no blast cells or promyelocytes in the blood, basophils are < 20%, and there is no extramedullary involvement.
Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1–35%), minor (36–65%), or minimal (66–95%). Major response (0–35%) includes both partial and complete responses.
Major molecular response criteria: A ≥ 3-log reduction in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse transcriptase PCR testing) in peripheral blood relative to a standardized baseline value.

The rates of complete hematologic response, major cytogenetic response, and complete cytogenetic response in first-line treatment were calculated using the Kaplan-Meier method, in which non-responses were censored at the time of the last examination. Using this approach, the cumulative response rates calculated for first-line imatinib treatment improved from 12 months to 84 months of treatment as follows: CHR increased from 96.4% to 98.4%, and CCR increased from 69.5% to 87.2%.

During the 7-year follow-up, there were 93 (16.8%) progression events in the imatinib group: 37 (6.7%) progressed to accelerated phase/blastic crisis (AP/BC), 31 (5.6%) lost a major cytogenetic response (MCR), 15 (2.7%) lost a complete hematologic response (CHR) or had an increase in WBC (white blood cell count), and 10 (1.8%) died from causes unrelated to CML. In contrast, the IFN+Ara-C group experienced 165 (29.8%) events, 130 of which occurred during first-line IFN+Ara-C therapy.

At 84 months, the estimated rate of patients who did not progress to the accelerated phase or blastic crisis was significantly higher in the imatinib group compared to the IFN group (92.5% vs. 85%, p < 0.001). The annual progression rate to the accelerated phase or blastic crisis decreased over time, dropping to less than 1% annually in the fourth and fifth years. The estimated progression-free survival rate at 84 months was 81.2% in the imatinib group and 60.6% in the control group (p < 0.001). The annual progression rates of any type for imatinib also declined over time.

In the imatinib and IFN+Ara-C groups, respectively, a total of 71 patients (12.8%) and 85 patients (15.4%) died. At 84 months, the estimated overall survival for the randomized imatinib and IFN+Ara-C groups was 86.4% (83–90) compared to 83.3% (80–87), respectively (p=0.073, log-rank test). The time-to-event endpoint is significantly influenced by the high crossover rate from IFN+Ara-C to imatinib.

The survival impact of imatinib treatment in chronic-phase newly diagnosed CML was thoroughly examined in a retrospective analysis, incorporating the imatinib data mentioned above with primary data from another Phase III trial using the same IFN+Ara-C regimen (n=325). This retrospective analysis demonstrated the superiority of imatinib over IFN+Ara-C in terms of overall survival (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 and molecular responses in imatinib-treated patients had a clear impact on

long-term outcomes. Among patients with CCR (or MCR) at 12 months, an estimated 96% (93%) did not progress to the accelerated phase/blastic crisis by 84 months, compared to only 81% of those without MCR at 12 months who remained free from advanced CML at 84 months (overall $p<0.001$, CCR vs. MCR $p=0.25$). Patients with at least a 3-log reduction in BCR-ABL transcripts at 12 months had a 99% probability of remaining progression-free at 84 months. Similar findings were identified based on the 18-month landmark analysis.

In this study, dose escalations from 400 mg to 600 mg daily, and subsequently from 600 mg to 800 mg daily, were allowed. After 42 months of follow-up, 11 patients experienced a confirmed loss of cytogenetic response (within 4 weeks). Of these 11 patients, the dose was increased to 800 mg daily in 4 cases, and 2 of these patients regained a cytogenetic response (1 partial and 1 complete; the patient with a complete response also achieved a molecular response). Among the 7 patients whose doses were not escalated, only one regained a complete cytogenetic response. Compared to the baseline patient population before dose escalation (n=551), the 40 patients whose doses were increased to 800 mg daily experienced a higher percentage of certain adverse reactions. Common adverse reactions included gastrointestinal hemorrhages, conjunctivitis, and elevations in transaminases or bilirubin. Other adverse events occurred at lower or equal frequencies.

Chronic Phase, Interferon Failure: A total of 532 patients were treated with an initial dose of 400 mg. These patients were divided into three main groups: hematologic failure (29%), cytogenetic failure (35%), or interferon intolerance (36%). Patients had previously received IFN therapy for a median duration of 14 months at doses of $\geq 25 \times 10^6$ IU/week, and all were in the late chronic phase, with a median time from diagnosis of 32 months. The primary efficacy variable of the study was the major cytogenetic response rate (complete plus partial responses, 0% to 35% Ph+ metaphases in the bone marrow).

In this study, 65% of patients achieved a major cytogenetic response; 53% (with a confirmed 43%) of these responses were complete (Table 3). A complete hematologic response was achieved in 95% of the patients.

Accelerated Phase: A total of 235 adult patients with accelerated-phase disease were enrolled. The first 77 patients were started on treatment with 400 mg daily; later, the study protocol was adjusted to allow for higher doses of imatinib, and the remaining 158 patients started with 600 mg of imatinib.

The primary efficacy variable was the rate of hematologic response, defined either as a complete hematologic response (no evidence of leukemia, i.e., clearance of blasts from the bone marrow and blood, but no improvement in all peripheral blood parameters for complete responses) or as a return to chronic-phase CML. A confirmed hematologic response was achieved in 71.5% of the patients (Table 3). Importantly, 27.7% of the patients also achieved a major cytogenetic response, and 20.4% of these responses were confirmed as complete (16% confirmed). For patients treated with 600 mg, the median progression-free survival and overall survival are currently estimated to be 22.9 and 42.5 months, respectively.

Myeloid Blast Crisis: A total of 260 patients with myeloid blast crisis were enrolled. Of these, 95 (37%) had previously received chemotherapy due to accelerated phase or blast crisis ("previously treated patients"), while 165 (63%) had not received chemotherapy previously ("previously untreated patients"). The first 37 patients started on 400 mg daily, after which the protocol was adjusted to allow higher doses, and the remaining 223 patients were started on 600 mg.

The primary efficacy variable was defined in the same way as in the accelerated phase study: the rate of hematologic response, either as a complete hematologic response, with no evidence of leukemia, or as a return to chronic phase. Hematologic response was achieved in 31% of patients in this study (36% in previously untreated patients, 22% in previously treated patients). The hematologic response rate was higher in patients treated with 600 mg imatinib compared to those treated with 400 mg (33% vs. 16%, p=0.022). The median overall survival for 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 hematologic response rate was found to be 70% within a 2-3 month period.

Table 5: Responses Achieved in Adult CML Studies

	Study 0110 – 37-month data, Chronic Phase, IFN Failure (n=532)	Study 0109 – 40.5-month data, Accelerated Phase (n=235)	Study 0102 – 38-month data, Myeloid Blast Crisis (n=260)
	Percentage of Patients (95% CI)		
Hematologic Response[1]	%95 (92.3-96.3)	%71 (65.3-77.2)	%31 (25.2-36.8)
Complete Hematologic 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 (22-33.9)	%15 (11.2-20.4)
Complete	%53	%20	%7
(Confirmed[3]) [%95 CI]	%43 (38.6 – 47.2)	%16 (11.3 – 21)	%2 (0.6 – 4.4)
Partial	%12	%7	%8

[1]Hematologic Response Criteria (all responses must be confirmed ≥4 weeks later):
CHR: Study 0110 [WBC count <10 x 10^9/L, platelet count <450 x 10^9/L, myelocytes + metamyelocytes <5%; no blasts or promyelocytes in blood; basophils <20%; no extramedullary involvement] and Study 0102 and 0109 [ANC ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, no blast cells in blood, BM blast cells <5%, and no extramedullary disease].
NEL: Same criteria as CHR; only ANC ≥1 x 10^9/L and platelet count ≥20 x 10^9/L (only for 0102 and 0109).
RTC: BM and PB blast cells <15%; BM and PB blast cells + promyelocyte ratio <30%; PB basophils ratio <20%; no extramedullary disease except spleen and liver (only for 0102 and 0109).
ANC = absolute neutrophil count, BM = bone marrow, PB = peripheral blood, WBC = leukocyte count
[2]Cytogenetic Response Criteria:
Major response includes both complete and partial responses:
Complete (0% Ph+ metaphases)
Partial (1–35%)
[3]Confirmed complete cytogenetic response by a second bone marrow cytogenetic assessment performed at least one month after the first bone marrow study.

Pediatric Population: A total of 26 pediatric patients under 18 years of age with chronic phase CML (n=11) or CML in blast crisis or Ph+ acute leukemias (n=15) were enrolled in a Phase I dose-escalation study. This population consisted of heavily pretreated patients: 46% had prior BMT, and 73% had prior multi-agent chemotherapy. Patients were treated with imatinib doses of 260 mg/m²/day (n=5), 340 mg/m²/day (n=9), 440 mg/m²/day (n=7), and 570 mg/m²/day (n=5). Of the 9 patients with

chronic phase CML and available cytogenetic data, 4 patients (44%) and 3 patients (33%) achieved complete and partial cytogenetic responses, respectively, resulting in a major cytogenetic response rate of 77%.

A total of 51 pediatric patients newly diagnosed with untreated chronic phase CML were enrolled in an open-label, multicenter, single-arm Phase II study. Patients were treated with 340 mg/m²/day imatinib without interruptions except for dose-limiting toxicity. Imatinib therapy achieved a rapid response in newly diagnosed pediatric CML patients, with a CHR rate of 78% after 8 weeks of treatment. The high CHR rate was accompanied by the development of complete cytogenetic response (CCR) in 65% of patients, a rate comparable to the results observed in adults. Additionally, partial cytogenetic response (PCR) was observed in 16% of patients, yielding a major cytogenetic response (MCR) of 81%. The vast majority of patients who achieved CCR did so between months 3 and 10, with a median time to response of 5.6 months according to Kaplan-Meier estimation.

The European Medicines Agency has waived the obligation to submit results of studies with imatinib in all subsets of the pediatric population with Philadelphia chromosome (BCR-ABL translocation) positive chronic phase chronic myeloid leukemia (for information regarding pediatric use, see Section 4.2).

Clinical studies for Ph+ ALL

Newly diagnosed Ph+ ALL:

In a controlled study (ADE10) comparing imatinib with chemotherapy induction in 55 newly diagnosed patients aged 55 and older, imatinib used as a single agent resulted in a significantly higher complete hematologic response rate compared to chemotherapy (96.3% versus 50%, p=0.0001). When imatinib was used as salvage therapy in patients who were non-responders or had a weak response to chemotherapy, 9 out of 11 patients (81.8%) achieved complete hematologic response. This clinical effect, observed after 2 weeks of treatment, was associated with a greater reduction in BCR-ABL transcripts in patients treated with imatinib compared to the chemotherapy arm (p=0.02). All patients received imatinib and consolidation chemotherapy after induction (see Table 4), and the levels of BCR-ABL transcripts were the same in both arms at the eighth week. As expected based on the study design, no differences were observed between the two groups in terms of remission duration, disease-free survival, or overall survival; however, in patients who achieved a complete molecular response and remained at a minimal residual disease level, both remission duration (p=0.01) and disease-free survival (p=0.02) outcomes were better.

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

Table 6: Chemotherapy Regimen Used in Combination with Imatinib

Study ADE10	
Pre-phase	DEX 10 mg/m² oral, days 1-5; CP 200 mg/m² IV, days 3, 4, 5; MTX 12 mg intrathecal, day 1.
Remission Induction	DEX 10 mg/m² oral, days 6-7, 13-16;

	VCR 1 mg/m² IV, days 7, 14; IDA 8 mg/m² IV (0.5 h), days 7, 8, 14, 15; CP 500 mg/m² IV (1 h), day 1; Ara-C 60 mg/m² IV, days 22-25, 29-32.
Consolidation Therapy I, III, V	MTX 500 mg/m² IV (24 h), days 1, 15; 6-MP 25 mg/m² oral, days 1-20.
Consolidation Therapy II, IV	Ara-C 75 mg/m² IV (1 h), days 1-5; VM26 60 mg/m² IV (1 h), days 1-5
Study AAU02	
Induction Therapy (*de novo* Ph+ ALL):	Daunorubicin 30 mg/m² IV, days 1-3, 15-16; VCR 2 mg total dose IV, days 1, 8, 15, 22; CP 750 mg/m² IV, days 1, 8; Prednisone 60 mg/m² oral, days 1-7, 15-21; IDA 9 mg/m² 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/m²/12 h IV (3 h), days 1-4; Mitoxantrone 10 mg/m² IV, days 3-5; MTX 15 mg intrathecal, day 1; Methylprednisolone 40 mg intrathecal, day 1.
Study ADE04	
Pre-phase	DEX 10 mg/m² oral, days 1-5; CP 200 mg/m² IV, days 3-5; MTX 15 mg intrathecal, day 1.
Induction Therapy I	DEX 10 mg/m² oral, days 1-5; VCR 2 mg IV, days 6, 13, 20; Daunorubicin 45 mg/m² IV, days 6-7, 13-14.
Induction Therapy II	CP 1 g/m² IV (1 h), days 26, 46; Ara-C 75 mg/m² IV (1 h), days 28-31, 35-38, 42-45; 6-MP 60 mg/m² oral, days 26-46.
Consolidation Therapy	DEX 10 mg/m² oral, days 1-5; Vindesine 3 mg/m² IV, day 1; MTX 1.5 g/m² IV (24 h), day 1; Etoposide 250 mg/m² IV (1 h), days 4-5; Ara-C 2 x 2 g/m² IV (3 h, q 12 h), day 5.
Study AJP01	
Induction Therapy	CP 1.2 g/m² IV (3 h), day 1; Daunorubicin 60 mg/m² IV (1 h), days 1-3; Vincristine 1.3 mg/m² IV, days 1, 8, 15, 21; Prednisolone 60 mg/m²/day oral.
Consolidation Therapy	Alternating chemotherapy course: MTX 1 g/m² IV (24 h) on day 1 with high-dose chemotherapy and for 4 cycles Ara-C 2 g/m² IV (q 12 h), days 2-3.
Maintenance	VCR 1.3 g/m² IV, day 1; Prednisolone 60 mg/m² oral, days 1-5.
Study AUS01	
Induction-	Hyper-CVAD regimen: CP 300 mg/m² IV (3 h, q 12 h), days 1-3;

Consolidation Therapy	Vincristine 2 mg IV, days 4, 11; Doxorubicin 50 mg/m² IV (24 h), day 4; Alternating DEX 40 mg/day, days 1-4 and 11-14, or MTX 1 g/m² IV (24 h), day 1, and Ara-C 1 g/m² IV (2 h, q 12 h), days 2-3 (total 8 cycles).
Maintenance	VCR 2 mg IV monthly for 13 months; Prednisolone 200 mg oral for 5 days monthly for 13 months.
All treatment regimens must include steroid administration for CNS prophylaxis.	
Abbreviations: Ara-C: cytosine arabinoside; CP: cyclophosphamide; DEX: dexamethasone; MTX: methotrexate; 6-MP: 6-mercaptopurine; VM26: teniposide; VCR: vincristine; IDA: idarubicin; IV: intravenous.	

Pediatric Population: In the I2301 study, a total of 93 pediatric, adolescent, and young adult patients (aged 1 to 22 years) with Ph+ ALL were enrolled in an open-label, multicenter, sequential cohort, non-randomized phase III study and treated with imatinib (340 mg/m²/day) in combination with intensive chemotherapy after induction therapy. In cohorts 1 to 5, imatinib was administered intermittently, with an increasing duration from cohort to cohort, and imatinib was started earlier: group 1 received the lowest intensity of imatinib, and group 5 received the highest intensity of imatinib (with the longest continuous daily imatinib exposure in days during the initial chemotherapy cycles). In cohort 5 patients (n=50), continuous daily exposure to imatinib during the early phases of treatment combined with chemotherapy increased 4-year event-free survival (EFS) compared to historical controls (n=120) who received standard chemotherapy without imatinib (69.6% versus 31.6%, respectively). The estimated 4-year OS in cohort 5 patients was 83.6%, compared to 44.8% in historical controls. Of the 50 patients in cohort 5, 20 (40%) underwent hematopoietic stem cell transplantation.

Table 7: Chemotherapy Regimen Used in Combination with Imatinib in Study I2301

Consolidation Block 1 (3 weeks)	VP-16 (100 mg/m²/day, IV): Days 1-5 Ifosfamide (1.8 g/m²/day, IV): Days 1-5 MESNA (360 mg/m²/dose every 3 hours, x 8 doses/day, IV): Days 1-5 G-CSF (5 mcgg/kg, SC): Days 6-15 or until ANC > 1500 after the lowest value IT Methotrexate (age-adjusted): ONLY Day 1 Triple IT Therapy (age-adjusted): Days 8, 15
Consolidation Block 2 (3 weeks)	Methotrexate (5 g/m² over 24 hours, IV): Day 1 Leucovorin (75 mg/m² at 36 hours, IV; 15 mg/m² IV or PO every 6 hours x 6 doses): Days 2 and 3 Triple IT Therapy (age-adjusted): Day 1 ARA-C (3 g/m²/dose q12h x 4, IV): Days 2 and 3 G-CSF (5 mcgg/kg, SC): Days 4-13 or until ANC > 1500 after the lowest value

Reinduction Block 1 (3 weeks)	VCR (1.5 mg/m²/day, IV): Days 1, 8, and 15 DAUN (45 mg/m²/day bolus, IV): Days 1 and 2 CPM (250 mg/m²/dose every 12 hours x 4 doses, IV): Days 3 and 4 PEG-ASP (2500 IU/m², IM): Day 4 G-CSF (5 mcgg/kg, SC): Days 5-14 or until ANC > 1500 after the lowest value Triple IT Therapy (age-adjusted): Days 1 and 15 DEX (6 mg/m²/day, PO): Days 1-7 and 15-21
Intensification Block 1 (9 weeks)	Methotrexate (5 g/m² over 24 hours, IV): Days 1 and 15 Leucovorin (75 mg/m² at 36 hours, IV; 15 mg/m² IV or PO every 6 hours x 6 doses): Days 2, 3, 16, and 17 Triple IT Therapy (age-adjusted): Days 1 and 22 VP-16 (100 mg/m²/day, IV): Days 22-26 CPM (300 mg/m²/day, IV): Days 22-26 MESNA (150 mg/m²/day, IV): Days 22-26 G-CSF (5 mcgg/kg, SC): Days 27-36 or until ANC > 1500 after the lowest value ARA-C (3 g/m² every 12 hours, IV): Days 43 and 44 L-ASP (6000 IU/m², IM): Day 44
Re-induction Block 2 (3 weeks)	VCR (1.5 mg/m²/day, IV): Days 1, 8, and 15 DAUN (45 mg/m²/day bolus, IV): Days 1 and 2 CPM (250 mg/m²/dose every 12 hours x 4 doses, IV): Days 3 and 4 PEG-ASP (2500 IU/m², IM): Day 4 G-CSF (5 mcgg/kg, SC): Days 5-14 or until ANC > 1500 after the lowest value Triple IT treatment (age-adjusted): Days 1 and 15 DEX (6 mg/m²/day, PO): Days 1-7 and 15-21
Consolidation Block 2 (9 weeks)	Methotrexate (5 g/m² every 24 hours, IV): Days 1 and 15 Leucovorin (75 mg/m² at 36 hours, IV; 15 mg/m² IV or PO every 6 hours x 6 doses): Days 2, 3, 16, and 17 Triple IT treatment (age-adjusted): Days 1 and 22 VP-16 (100 mg/m²/day, IV): Days 22-26 CPM (300 mg/m²/day, IV): Days 22-26 MESNA (150 mg/m²/day, IV): Days 22-26 G-CSF (5 mcgg/kg, SC): Days 27-36 or until ANC > 1500 after the lowest value ARA-C (3 g/m², every 12 hours, IV): Days 43 and 44 L-ASP (6000 IU/m², IM): Day 44

Maintenance (8-week cycles) Cycle 1-4	MTX (5 g/m² every 24 hours, IV): Day 1 Leucovorin (75 mg/m² at 36 hours, IV; 15 mg/m² IV or PO every 6 hours x 6 doses): Days 2 and 3 Triple IT treatment (age-adjusted): Days 1 and 29 VCR (1.5 mg/m², IV): Days 1 and 29 DEX (6 mg/m²/day PO): Days 1-5; 29-33 6-MP (75 mg/m²/day, PO): Days 8-28 Methotrexate (20 mg/m²/week, PO): Days 8, 15, and 22 VP-16 (100 mg/m², IV): Days 29-33 CPM (300 mg/m², IV): Days 29-33 MESNA IV: Days 29-33 G-CSF (5 mcgg/kg, SC): Days 34-43
Maintenance (8-week cycles) Cycle 5	Cranial Irradiation (only Block 5) For all patients with CNS1 and CNS2 at diagnosis: 12 Gy in 8 fractions For patients with CNS3 at diagnosis: 18 Gy in 10 fractions VCR (1.5 mg/m²/day, IV): Days 1 and 29 DEX (6 mg/m²/day, PO): Days 1-5; 29-33 6-MP (75 mg/m²/day, PO): Days 11-56 (Starting on Day 1 of Cycle 5, 6-MP is stopped during the 6-10 days of cranial irradiation. 6-MP is resumed on Day 1 after cranial irradiation is completed.) Methotrexate (20 mg/m²/week, PO): Days 8, 15, 22, 29, 36, 43, and 50
Maintenance (8-week cycles) Cycles 6-12	VCR (1.5 mg/m²/day, IV): Days 1 and 29 DEX (6 mg/m²/day, PO): Days 1-5; 29-33 6-MP (75 mg/m²/day, PO): Days 1-56 Methotrexate (20 mg/m²/week, PO): Days 1, 8, 15, 22, 29, 36, 43, and 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 <0.1 mcgM q6h = Every 6 hours Gy = Gray

Study AIT07 is a multicenter, open-label, randomized, Phase II/III study involving 128 patients (aged 1 to <18 years) treated with imatinib in combination with chemotherapy. The safety data obtained from this study are consistent with the safety profile of imatinib in Ph+ ALL patients.

Relapsed/chemotherapy-refractory Ph+ ALL
When imatinib is used as a single agent in relapsed/refractory Ph+ ALL patients, response could be evaluated in 53 out of 411 patients, with a hematologic response rate of 30% (9% complete) and a major cytogenetic response rate of 23%. (Note: 353 of the 411 patients were treated in an expanded access study without primary response data collected). In the total population of 411 relapsed/refractory Ph+ ALL patients, the median progression-free survival was between 2.6 and 3.1

months, while the median overall survival in evaluable patients (401 patients) was between 4.9 and 9 months. These results were similar when reanalyzed with the inclusion of patients aged 55 and older.

Clinical trials in MDS/MPD
Experience with imatinib in this indication is very limited and is based on hematologic and cytogenetic response rates. There is no controlled study demonstrating clinical benefit or increased survival. An open-label, multicenter, Phase II clinical study (Study B2225) has been conducted in various patient populations suffering from life-threatening diseases associated with Abl, Kit, or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD treated with 400 mg of imatinib daily. Three patients achieved a complete hematologic response (CHR) and one patient had a partial hematologic response (PHR). In the original analysis, hematologic responses (2 CHR and 1 PHR) were observed in three of the four patients with PDGFR gene rearrangements. The ages of these patients ranged from 20 to 72 years.

A long-term safety and efficacy data collection observational registry study (Study L2401) was conducted for patients suffering from myeloproliferative neoplasms with PDGFR-β gene rearrangement treated with imatinib. In this registry study, 23 patients received a median dose of 264 mg daily (range: 100 to 400 mg) of imatinib for a median duration of 7.2 years (range: 0.1 to 12.7 years). Due to the observational nature of this registry study, hematologic, cytogenetic, and molecular evaluation data are available for 22, 9, and 17 patients, respectively, out of the 23 enrolled patients. Conservatively assuming that patients with missing data did not respond, a hematologic response (CHR) was observed in 20/23 (87%) patients, a cytogenetic response (CYR) in 9/23 (39.1%) patients, and a molecular response (MR) in 11/23 (47.8%) patients. When the response rates were calculated for patients with at least one valid evaluation, the response rates were 20/22 (90.9%) for CHR, 9/9 (100%) for CYR, and 11/17 (64.7%) for MR.

Additionally, 24 more patients with MDS/MPD have been reported in 13 publications. 21 patients were treated with 400 mg of imatinib daily, while the other 3 patients received lower doses. PDGFR gene rearrangements were detected in 11 patients, of whom 9 achieved CHR and 1 achieved partial hematologic response (PHR). The ages of these patients ranged from 2 to 79 years. A recent publication revealed updated information on these 11 patients, showing that all of them remained in cytogenetic remission (ranging from 32 to 38 months). The same publication reported long-term follow-up data on 12 MDS/MPD patients with PDGFR gene rearrangements (5 patients from the B2225 study). These patients received a median of 47 months (range: 24 days to 60 months) of imatinib. For six of these patients, the follow-up period is now over 4 years. Eleven patients achieved rapid CHR; when measured by RT-PCR, 10 of them showed complete resolution of cytogenetic abnormalities, and fusion transcripts decreased or disappeared. Hematologic and cytogenetic responses were maintained for a median of 49 months (range: 19-60 months) and 47 months (range: 16-59 months), respectively. The overall survival since diagnosis is 65 months (range: 25-234 months). Imatinib administration in patients without genetic translocation generally does not provide any improvement.

There are no controlled studies in pediatric patients with MDS/MPD. Five patients with MDS/MPD related to PDGFR gene rearrangements have been reported in four publications. The ages of these patients ranged from 3 months to 4 years, and imatinib was given at doses of 50 mg daily or doses ranging from 92.5 to 340 mg/m² daily. All patients achieved complete hematologic response, cytogenetic response, and/or clinical response.

Clinical Studies Related to HES/CEL

An open-label, multicenter phase II clinical study (Study B2225) was conducted to test imatinib in various patient populations 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 imatinib at doses ranging from 100 mg to 1000 mg daily. Additionally, 162 patients with HES/CEL, reported in 35 case reports and case series, were treated with imatinib at doses ranging from 75 mg to 800 mg daily. Cytogenetic abnormalities were evaluated in 117 of the total 176 patients. FIP1L1-PDGFRα fusion kinase was identified in 61 of these 117 patients. In three other published reports, four additional HES patients were found to be FIP1L1-PDGFRα positive. All 65 FIP1L1-PDGFRα fusion kinase-positive patients achieved a sustained complete hematologic response (CHR) for months (ranging from 1+ to 44+ months during reporting). As reported in a recent publication, 21 of these 65 patients achieved complete molecular remission with a median follow-up of 28 months (range: 13 to 67 months). The ages of these patients ranged from 25 to 72 years. Additionally, the investigators reported developments in symptomatology and other organ dysfunction abnormalities in case reports. Developments were reported in heart, nerve, skin/subcutaneous tissue, respiratory/chest/mediastinal, musculoskeletal/connective tissue/vascular, and gastrointestinal organ systems.

There are no controlled studies in pediatric patients with HES/CEL. Three publications reported on three patients with HES and CEL associated with PDGFR gene rearrangements. The ages of these patients ranged from 2 to 16 years, and imatinib was administered at doses of 300 mg/m² daily or varying doses between 200 mg and 400 mg daily. All patients achieved complete hematologic response, complete cytogenetic response, and/or complete molecular response.

Clinical Studies in Unresectable and/or Metastatic GIST

A phase II, open-label, randomized, uncontrolled multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). 147 patients were enrolled in this study and randomized to receive either 400 mg or 600 mg of imatinib once daily for 36 months. The ages of these patients ranged from 18 to 83 years, and they had pathologically confirmed unresectable and/or metastatic Kit-positive malignant GIST. The analysis was routinely conducted after antigen retrieval using an immunohistochemistry Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) and the avidin-biotin-peroxidase complex method.

The primary efficacy evidence was based on objective response rates. Tumors were required to be measurable in at least one disease region, and the response characterization was based on Southwest Oncology Group (SWOG) criteria. The results are presented in Table 8.

Table 8: Best Tumor Response in the STIB2222-coded GIST Study

	All Dose Groups (n=147)
	400 mg n= 73 **600 mg n=74**
Best Response	**n (%)**
Complete Response	1 (0.7)
Partial Response	98 (66.7)
Stable Disease	23 (15.6)
Progressive Disease	18 (12.2)
Not Assessable	5 (3.4)
Unknown	2 (1.4)

There were no differences in response rates between the two dose groups. In the interim analysis, a significant number of patients with stable disease achieved partial response with longer treatment (median follow-up duration: 31 months). The median time to response was 13 weeks (95% CI: 12-23). For responders, the median time until treatment failure was 122 weeks (95% CI: 106-147), while the median time in the overall study population was 84 weeks (95% CI: 71-109). A median overall survival estimate has not been reached. After 36 months of follow-up, the Kaplan-Meier survival estimate is 68%.

In two clinical studies (study B2222 and intergroup study S0033), the daily dose of imatinib was increased to 800 mg in patients who progressed on lower daily doses of 400 mg or 600 mg. The dose was increased to 800 mg in a total of 103 patients; after the dose escalation, 6 patients achieved partial response and 21 patients achieved disease stabilization, resulting in an overall clinical benefit of 26%. Based on the available safety data, increasing the dose to 800 mg per day in patients who progressed on lower daily doses of 400 mg or 600 mg did not appear to affect the safety profile of imatinib.

Adjuvant GIST Clinical Studies
Imatinib in adjuvant treatment conditions has been investigated in a multicenter, 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 diagnosed with primary GIST expressing Kit protein via immunohistochemistry, with a tumor size of ≥3 cm at the largest site, and who underwent complete gross resection of the primary GIST within 14-70 days prior to enrollment in the study, were included. After the primary GIST was resected, patients were randomized to one of two groups: imatinib 400 mg/day for one year or placebo.

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

Imatinib significantly prolonged RFS, with 75% of patients in the imatinib group being recurrence-free at month 38, while 75% of patients in the placebo group remained recurrence-free at month 20 (95% CI [30-not calculable]; [14-not calculable]); hazard ratio = 0.398 [0.259-0.610], p<0.0001). At the end of one year, the overall RFS was significantly better for imatinib (97.7%) compared to placebo (82.3%) (p<0.0001). Thus, the risk of recurrence was reduced by 89% in the imatinib group compared to the placebo group (hazard ratio = 0.113 [0.049-0.264]).

The risk of recurrence after surgery for primary GIST was retrospectively evaluated based on prognostic factors: tumor size, mitotic index, and tumor location. Mitotic index data were available for 556 of the 713 patients in the treatment population (ITT). The results of subgroup analyses based on the NIH (National Institutes of Health) and AFIP (Armed Forces Institute of Pathology) risk classifications are shown in Table 9. No benefit was observed in the low and very low-risk groups. No overall survival benefit was observed.

Table 9: Z9001 study RFS analysis summary according to NIH and AFIP risk classification

Risk Criteria	Risk Level	Percentage of Patients (%)	Event Count/Patient Count	Overall Hazard Ratio (95% CI)*		RFS Rates (%)
			Imatinib vs Placebo		12-month	24-month
					Imatinib vs Placebo	Imatinib vs Placebo
NIH	Low	29.5	0/86 vs 2/90	NE.	100 vs	100 vs

					98.7	95.5
	Moderate	25.7	4/75 vs 6/78	0.59 (0.17;2.1)	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	80.7 vs 46.6
AFIP	Very Low	20.7	0/52 vs 2/63	NE.	100 vs 98.1	100 vs 93
	Low	25	2/70 vs 0/69	NE.	100 vs 100	97.8 vs 100
	Moderate	24.6	2/70 vs 11/67	0.16 (0.03;0.7)	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

In a second multicenter, open-label Phase III study (SSG XVIII/AIO), postoperative patients with surgical GIST resection and one of the following conditions were treated with 400 mg/day imatinib for 12 months compared to 36 months: tumor diameter > 5 cm and mitotic count > 5/50 high power field (HPF); or tumor diameter > 10 cm with any mitotic count or mitotic count > 10/50 HPF for any size tumor or tumors that ruptured into the peritoneal cavity. A total of 397 patients were enrolled, and these patients were randomized into the study (199 patients in the 12-month arm and 198 patients in the 36-month arm), with a median age of 61 years (range 22 to 84 years). The median follow-up duration was 54 months (from randomization to data cutoff date), with the median duration from the first patient's randomization to the data cutoff date being 83 months.

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

36 months of imatinib treatment resulted in a significant extension of RFS compared to 12 months of imatinib treatment (overall hazard ratio (HR) = 0.46 [0.32, 0.65], p<0.0001) (Table 8, Figure 1).

Additionally, 36 months of imatinib treatment significantly extended 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 treatment duration (>36 months) may delay the occurrence of new recurrences; however, the impact of this finding on overall survival is still unknown.

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

36 months of treatment with imatinib was superior to 12 months of treatment in the ITT (Intention-to-Treat) analysis, which included the entire study population. In a planned subgroup analysis based on mutation type, patients with exon 11 mutations had a hazard ratio of 0.35 for RFS with 36 months of treatment (95% CI: 0.22, 0.56).

Due to the low number of observed events, no conclusions can be drawn for less common mutation subgroups.

Table 10: 12 months and 36 months Imatinib Treatment (SSGXVIII/AIO Study)

	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)	90.7 (85.6-94)
36 months	60.1 (52.5-66.9)	86.6 (80.8-90.8)
48 months	52.3 (44-59.8)	78.3 (70.8-84.1)
60 months	47.9 (39-56.3)	65.6 (56.1-73.4)
Survival		
36 months	94 (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 (73-87.8)	92 (85.3-95.7)

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

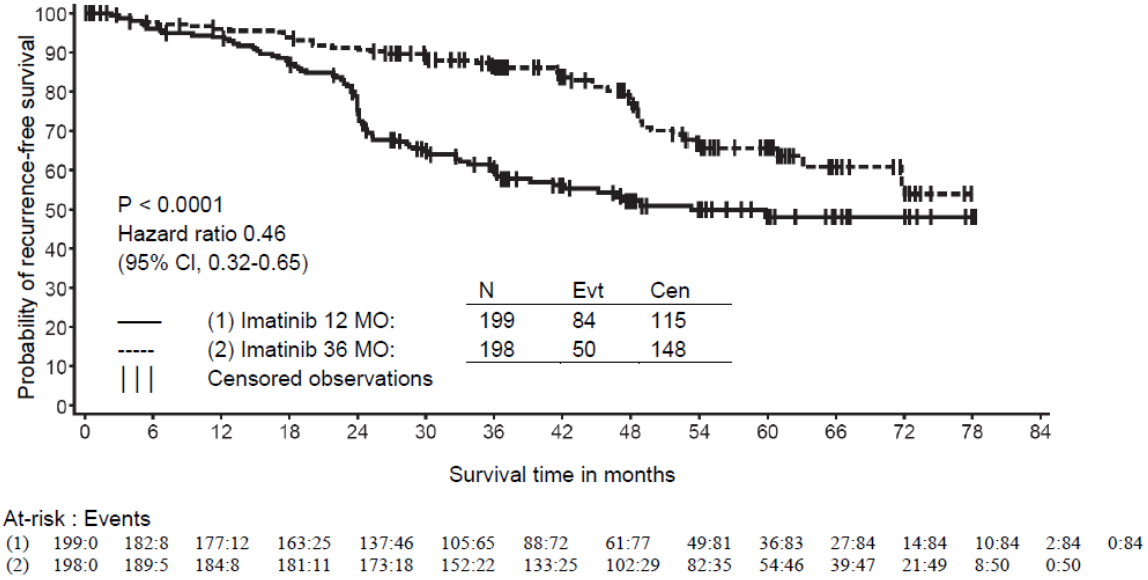
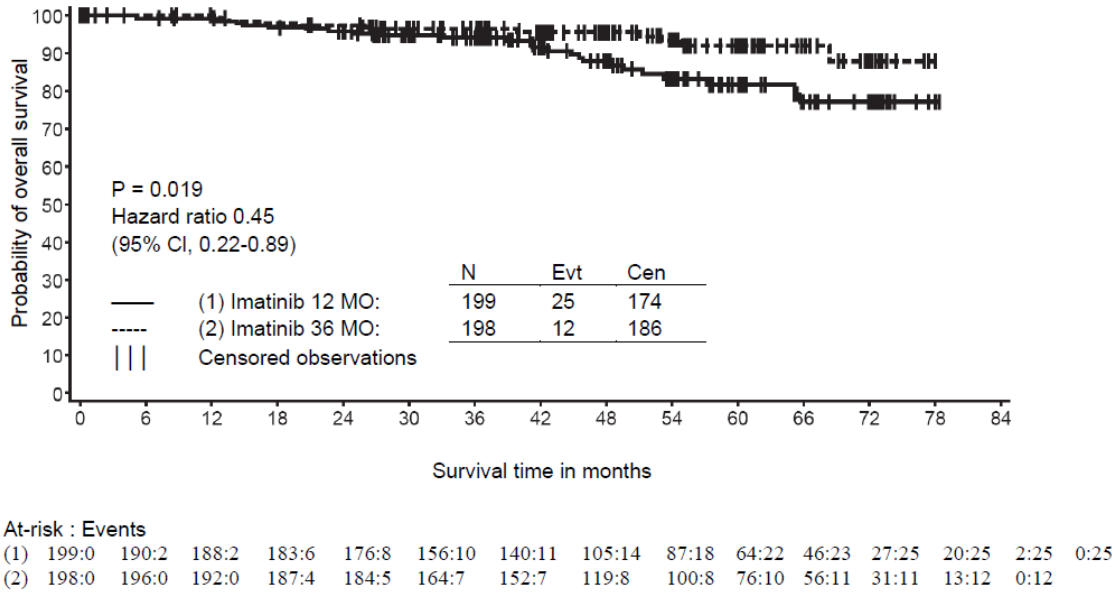


Figure 2: Kaplan-Meier estimates for overall survival (ITT population)



At-risk : Events

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

There are no controlled studies on pediatric patients with c-Kit positive GIST. A study has reported seventeen (17) patients with GIST (with or without Kit and PDGFR mutations). These patients were aged between 8 and 18 years, and imatinib was administered in doses ranging from 300 to 800 mg daily, both in adjuvant and metastatic conditions. Most of the pediatric patients with GIST did not have confirmed data for c-Kit or PDGFR mutations, which may have led to mixed clinical outcomes.

Clinical studies in DFSP

A phase II, open-label, multicenter clinical trial (study B2225) involving 12 patients with DFSP treated with 800 mg of imatinib daily was conducted. The ages of the DFSP patients ranged from 23 to 75; the DFSP was metastatic, recurred locally after the first resective surgery, and was deemed not suitable for further resective surgery at the time of entry into the study. The primary evidence for efficacy was based on objective response rates. Of the 12 registered patients, 9 responded, including 1 complete response and 8 partial responses. Of the partial responders, 3 were later rendered disease-free by surgery. In the B2225 study, the median treatment duration was 6.2 months, with a maximum duration of 24.3 months. In 5 published case reports, 6 additional DFSP patients treated with imatinib were described, with ages ranging from 18 months to 49 years. The adult patients in the published literature were treated with 400 mg (4 cases) or 800 mg (1 case) of imatinib daily. Of these, 3 had a complete response and 2 had a partial response. The median treatment duration in the published literature ranged from 4 weeks to more than 20 months. Nearly all patients who responded to imatinib treatment had a translocation t(17:22)[(q22:q13)] or its gene product.

There are no controlled studies in pediatric patients with DFSP. Five (5) patients with DFSP and PDGFR gene rearrangements have been reported in three publications. The ages of these patients range from neonates to 14 years, and imatinib was administered in doses ranging from 50 mg daily or 400 to 520 mg/m² daily. All patients achieved partial and/or complete responses.

5.2. Pharmacokinetic properties

General Principles

The pharmacokinetics of imatinib have been evaluated over a dose range of 25 - 1000 mg. Plasma

pharmacokinetic profiles were analyzed on Day 1 and on Day 7 or 28 when steady-state plasma levels were reached.

Absorption
The average absolute bioavailability of imatinib is 98%. Following an oral dose, there was a high interpatient variability in the area under the plasma concentration-time curve (AUC) values. When administered with a high-fat meal, the absorption rate of imatinib decreased minimally (an 11% decrease in C_{max} and a 1.5-hour delay in T_{max}), and a small reduction (7.4%) in the AUC was observed compared to fasting conditions. The effect of previous gastrointestinal surgery on drug absorption has not been studied.

Distribution
The binding of imatinib at clinically relevant concentrations to plasma proteins was approximately 95% and, on the basis of *in vitro* assays, was mainly bound to albumin and alpha-acid-glycoprotein and to small amounts to lipoprotein.

Biotransformation-
In humans, the major circulating metabolite is an N-demethylated piperazine derivative that exhibits similar *in vitro* activity to the parent drug. It has been found that the AUC of this metabolite is only 16% of that of imatinib. The binding of the N-demethylated metabolite to plasma proteins is similar to that of the parent compound.

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

In vitro results showed that CYP3A4 is the primary P450 enzyme catalyzing the biotransformation of imatinib. Among a panel of potential concomitant drugs (acetaminophen, acyclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V), only erythromycin (IC50 50 mcgM) and fluconazole (IC50 118 mcgM) showed clinically significant inhibition of imatinib metabolism.

Under *in vitro* conditions, it was demonstrated that imatinib is a competitive inhibitor of the marker substrates of CYP2C9, CYP2D6, and CYP3A4/5. Ki values in human liver microsomes were found to be 27, 7.5, and 7.9 mcgmol/L, respectively. In patients, the maximal plasma concentrations of imatinib are 2-4 mcgmol/L, so inhibition of CYP2D6 and/or CYP3A4/5 mediated metabolism by concomitant drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil but inhibited the metabolism of paclitaxel due to competitive CYP2C8 inhibition (Ki = 34.7 mcgM). This Ki value is much higher than the expected plasma levels of imatinib in patients, so no interaction is expected when 5-fluorouracil or paclitaxel is used concomitantly with imatinib.

Elimination
Following an oral dose of 14C-labeled imatinib, based on the detection of the compound(s), approximately 81% of the dose was recovered within 7 days, with 68% in feces and 13% in urine. Unchanged imatinib accounted for 25% of the dose (5% in urine, 20% in feces), and the remainder consisted of metabolites.

Plasma pharmacokinetics
After oral administration in healthy volunteers, the half-life (t1/2) of imatinib was approximately 18 hours, suggesting that once-daily dosing is appropriate. After administering 25-1000 mg of imatinib

orally, the increase in AUC with increasing doses followed a linear pattern. No change in imatinib kinetics was observed with repeated doses, and when administered once daily, the accumulation at steady state was 1.5 to 2.5 times higher.

Pharmacokinetics in GIST Patients
In GIST patients, the steady-state exposure was 1.5 times higher than that observed in CML patients receiving the same dose (400 mg/day). Based on pharmacokinetic analysis of the GIST patient population, three variables (albumin, WBC, and bilirubin) were found to have a significant relationship with imatinib pharmacokinetics. Lower albumin levels resulted in lower clearance (CL/f), and higher WBC levels caused a decrease in CL/f. However, these relationships did not appear significant enough to require dose adjustments. The presence of hepatic metastases in this patient population could potentially lead to liver failure and reduced metabolism.

Population Pharmacokinetics
According to population pharmacokinetic analyses in CML patients, age has a small effect on the volume of distribution (>12% increase in patients over 65 years old). This change is considered not clinically significant. Regarding the effect of body weight on imatinib clearance, for a person weighing 50 kg, the clearance is expected to be 8.5 L/s, while for a person weighing 100 kg, the clearance increases to 11.8 L/s. These changes were not considered sufficient to require a dose adjustment based on body weight. Gender had no effect on imatinib kinetics.

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. The exposure values obtained with 260 and 340 mg/m² of imatinib in children were similar to those obtained with 400 and 600 mg of imatinib in adults, respectively. The $AUC_{(0\text{-}24\ hours)}$ values for 340 mg/m² imatinib on the first and eighth days showed that the drug accumulated 1.7 times after repeated once-daily doses.

In pediatric patients with hematological disorders (CML, Ph+ALL, or other hematological disorders treated with imatinib), based on combined population pharmacokinetics analysis, imatinib clearance increases in parallel with body surface area (BSA). After adjusting for BSA, other demographic factors such as age, body weight, and body mass index did not have clinically significant effects on imatinib exposure. The analysis confirmed that in pediatric patients, imatinib exposure after once-daily doses of 260 mg/m² (not exceeding 400 mg per day) or 340 mg/m² (not exceeding 600 mg per day) is similar to that in adult patients receiving once-daily doses of 400 mg or 600 mg imatinib.

Organ Dysfunction
Imatinib and its metabolites are not significantly eliminated through the kidneys. Patients with mild to moderate kidney dysfunction appear to have higher plasma levels than those with normal kidney function. The increase is approximately 1.5 to 2 times and corresponds to a 1.5-fold increase in plasma alpha-1 acid glycoprotein (AGP) levels, to which imatinib strongly binds. In patients with kidney dysfunction, the free drug clearance of imatinib is likely similar to that in patients with normal kidney function because renal excretion constitutes a minor elimination pathway for imatinib (see sections 4.2 and 4.4).

Although pharmacokinetic analysis results indicate variability between individuals, the average imatinib exposure in patients with varying degrees of liver insufficiency did not increase compared to patients with normal liver function (see sections 4.2, 4.4, and 4.8).

5.3. Preclinical safety data

The preclinical safety of imatinib has been evaluated in rats, dogs, monkeys, and rabbits.

In repeated dose toxicity studies, mild to moderate hematological changes were observed in rats, dogs, and monkeys, with bone marrow changes accompanying these alterations in rats and dogs.

The liver was the target organ in rats and dogs. In both species, mild to moderate increases in transaminases, as well as slight decreases in cholesterol, triglycerides, total protein, and albumin levels, were observed. No changes were observed in the rat liver. In dogs treated for two weeks, elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia were observed, indicating severe liver toxicity.

In monkeys treated for two weeks, renal toxicity was observed, characterized by focal mineralization, dilation of renal tubules, and tubular necrosis. Several of these animals showed increases in blood urea nitrogen (BUN) and creatinine. In a 13-week study, rats treated with doses ≥6 mg/kg showed transitional epithelial hyperplasia in the bladder and renal papilla without changes in serum or urine parameters. Chronic imatinib treatment was associated with an increased incidence of opportunistic infections.

In a 39-week monkey study, the NOAEL (No Observed Adverse Effect Level) was determined to be 15 mg/kg, the lowest dose, which is approximately one-third of the maximum human dose of 800 mg based on body surface area. Treatment in these animals resulted in worsening of normally suppressed malarial infections.

Imatinib did not show genotoxic effects in an *in vitro* bacterial cell test (Ames test), an in vitro mammalian cell test (mouse lymphoma), or an in vivo rat micronucleus test. However, in the presence of metabolic activation, positive genotoxic effects (chromosomal aberration) were observed in an in vitro mammalian cell test (Chinese hamster ovary). Two intermediates present in the final product, derived from the manufacturing process, tested positive for mutagenicity in the Ames test. One of these intermediates also gave positive results in the mouse lymphoma test.

In a fertility study, male rats administered doses for 70 days before mating showed a decrease in testicular and epididymal weights and the percentage of motile sperm at a dose of 60 mg/kg, which is approximately equal to the maximum clinical dose of 800 mg/day based on body surface area. This effect was not observed at doses ≤ 20 mg/kg. In dogs, oral doses ≥ 30 mg/kg also showed a mild to moderate reduction in spermatogenesis. In female rats, no effects were observed on mating or pregnancy when doses were administered for 14 days before mating and until day 6 of gestation. At a dose of 60 mg/kg, there was a significant decrease in implantation-related fetal loss and the number of live fetuses. This effect was not observed at doses ≤ 20 mg/kg.

In an oral prenatal and postnatal development study conducted in rats, red vaginal discharge was recorded on day 14 or 15 of gestation in the 45 mg/kg/day group. The number of stillborn pups and the number of pups dying between days 0-4 post-birth also increased at this dose. In the F1 pups, average body weights decreased during the period from birth to euthanasia, and the number of pups reaching the preputial separation criterion was slightly reduced. At the 45 mg/kg/day dose, F1 fertility was not affected, but there was an increase in resorption and a decrease in the number of live fetuses. The No Observed Effect Level (NOEL) for both the mother animals and the F1 generation was 15 mg/kg/day (one-quarter of the maximum human dose of 800 mg).

Imatinib, when administered at doses ≥ 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, showed teratogenic effects during organogenesis in

rats. Teratogenic effects included exencephaly or encephalocele, absence/incompleteness of the frontal bones, and absence of the parietal bones. These effects were not observed at doses ≤ 30 mg/kg.

In a juvenile development toxicity study in rats (postnatal days 10 to 70), no new target organs were identified according to known target organs. In the juvenile toxicity study, at levels approximately 0.3 to 2 times the maximum recommended pediatric exposure dose of 340 mg/m², transient effects on growth, as well as delays in vaginal opening and preputial separation, were observed. Additionally, at levels approximately 2 times the recommended maximum pediatric exposure dose of 340 mg/m², mortality was observed in juvenile animals (approximately during weaning).

In a 2-year rat carcinogenicity study, imatinib administered at doses of 15, 30, and 60 mg/kg/day resulted in a statistically significant reduction in lifespan in males at 60 mg/kg/day and in females at ≥ 30 mg/kg/day. Histopathological examination of deceased animals revealed cardiomyopathy (in both sexes), chronic progressive nephropathy (in females), and preputial gland papilloma as the primary cause of death or euthanasia. The target organs for neoplastic changes were the kidneys, bladder, urethra, preputial and clitoral glands, small intestine, parathyroid glands, adrenal glands, and non-glandular stomach.

Papilloma/carcinoma in the preputial/clitoral glands were observed from the dose of 30 mg/kg/day, corresponding to 0.5 or 0.3 times the human daily exposure (on an EAA basis) at 400 mg/day or 800 mg/day, or 0.4 times the daily exposure in children at a dose of 340 mg/m²/day (on an EAA basis). The No Observed Effect Level (NOEL) was 15 mg/kg/day. At doses of 400 mg/day or 800 mg/day, corresponding to 1.7 or 1 times the human daily exposure (on an EAA basis), or 1.2 times the daily exposure in children at a dose of 340 mg/m²/day (on an EAA basis), renal adenomas/carcinomas, bladder and urethra papillomas, small intestine adenocarcinomas, parathyroid adenomas, benign and malignant adrenal medullary tumors, and non-glandular stomach papillomas/carcinomas were observed. The NOEL was 30 mg/kg/day.

The mechanism and significance of these findings in the rat carcinogenicity study for humans have not yet been clarified.
Non-neoplastic lesions not identified in early clinical studies were related to the cardiovascular system, pancreas, endocrine organs, and teeth. The most significant changes included cardiac hypertrophy and dilation, leading to signs of heart failure in some animals.

The active substance imatinib poses an environmental risk for sedimentary layer organisms.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Microcrystalline cellulose
Hydroxypropyl methylcellulose
Crospovidone
Colloidal silicon dioxide
Magnesium stearate

Film coating [TF 276U280002 White]
Calcium carbonate
Hpmc 2910/Hypromellose
Isomalt

Medium-chain triglyceride (vegetable)

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.
Each cardboard box contains 30 tablets and a package leaflet.

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

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)
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