SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Imanitib 100 mg film-coated tablets
Imarem 100

Imanitib 400 mg film-coated tablets
Imarem 400

2. Qualitative and quantitative composition
Imarem 100
Each film-coated tablet contains imatinib mesilate equivalent to 100 mg imatinib.

Imarem 400
Each film-coated tablet contains imatinib mesilate equivalent to 400 mg imatinib.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet

Imarem 100
Dark yellow to brownish-orange, round-shaped, film-coated tablets with a break line on one side and '100' on the other side.

Imarem 400
Dark yellow to brownish-orange, round-shaped, film-coated tablets with a break line on one side and '400' on the other side.

The tablet can be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications
Imatinib is indicated for the treatment of

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

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic DFSP. 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.

4.2 Posology and method of administration

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

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

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

Posology for CML in adult patients

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

Treatment duration: The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.

Dose increases from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients with blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response.

Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for CML in children

Dosing for children should be on the basis of body surface area (mg/m2). The dose of 340 mg/m2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800 mg). Treatment can be given as a once daily dose, or alternatively, the daily dose may be split into two administrations – one in the morning and one in the evening. The dose recommendation is currently based on a small number of paediatric patients (see sections 5.1 and 5.2).

There is no experience with the treatment of children below 2 years of age.

Dose increases from 340 mg/m2 daily to 570 mg/m2 daily (not to exceed the total dose of 800 mg) may be considered in children in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

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

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

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

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

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

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

Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. Treatment should be continued as long as the patient continues to benefit.

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

<u>Dose adjustment for adverse reactions</u>

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

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

Haematological adverse reactions
Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia:

HES/CEL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at previous dose (i.e., before severe adverse reaction).
Chronic phase CML, MDS/MPD (starting dose 400 mg) HES/CEL (at dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at previous dose (i.e., before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume imatinib at reduced dose of 300 mg.
Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at previous dose (i.e., before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume imatinib at reduced dose of 260 mg/m^2.
Blast crisis CML and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of imatinib to 400 mg. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop imatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of imatinib to 260 mg/m^2. 3. If cytopenia persists for 2 weeks, reduce further to 200 mg/m^2. 4. If cytopenia persists for 4 weeks and is still
		unrelated to leukaemia, stop imatinib until ANC ≥1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 200 mg/m^2.

DFSP (at dose 800 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at 600 mg. 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume imatinib at reduced dose of 400 mg.
ANC = absolute neutrophil count		
[a] occurring after at least 1 month of treatment		

Special populations

Paediatric use
There is no experience in children with CML below 2 years of age (see section 5.1). There is very limited experience in children with MDS/MPD, DFSP and HES/CEL.

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

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

Liver dysfunction classification:

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

ULN = upper limit of normal for the institution
AST = aspartate aminotransferase

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

Hypothyroidism

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

Hepatotoxicity

Metabolism of imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2, 4.8 and 5.2).

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.5 and 4.8).

Fluid retention

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

Patients with cardiac disease

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

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

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

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

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

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

Patients should be tested for HBV infection before initiating treatment with imatinib. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with imatinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

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

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

Laboratory tests
Complete blood counts must be performed regularly during therapy with imatinib. Treatment of CML patients with imatinib has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is likely to be related to the stage of the disease

being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with imatinib may be interrupted or the dose may be reduced, as recommended in section 4.2. Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib.

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

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

Paediatric population
There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. In an observational study in the CML paediatric population, a statistically significant decrease (but of uncertain clinical relevance) in median height standard deviation scores after 12 and 24 months of treatment was reported in two small subsets irrespective of pubertal status or gender. Close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

*Active substances that may **increase** imatinib plasma concentrations*
Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g., protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) could decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (the mean C_{max} and AUC of imatinib rose by 26% and 40%, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering imatinib with inhibitors of the CYP3A4 family.

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

Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.

Active substances that may have their plasma concentration altered by imatinib
Imatinib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g., cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). Imatinib may increase plasma concentration of other CYP3A4 metabolised drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e., statins, etc.).

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

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

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

Caution should therefore be exercised when using high doses of imatinib and paracetamol concomitantly.

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

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

4.6 Pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must be advised to use effective contraception during treatment.

Pregnancy
There is limited data on the use of imatinib in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who

have taken imatinib. Studies in animals have however shown reproductive toxicity (see section 5.3) and the potential risk for the foetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breastfeeding
There is limited information on imatinib distribution on human milk. Studies in two breast-feeding women revealed that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking imatinib should not breast-feed.

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

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

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

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

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

When imatinib was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed.

Considering the limited safety database, the adverse events thus far reported in children are consistent with the known safety profile in adult patients with Ph+ ALL. The safety database for children with Ph+ ALL is very limited, though no new safety concerns have been identified.

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

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

Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first. Adverse reactions and their frequencies are reported in Table 1.

Table 1. Tabulated summary of adverse reactions

Infections and infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1],sinusitis, cellulitis, upper respiratory tract infection, influenza,
	urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Not known	Hepatitis B reactivation*
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour lysis syndrome
Not known:	Tumour haemorrhage/tumour necrosis*
Immune system disorders	
Not known:	Anaphylactic shock*
Blood and lymphatic system disorders	
Very common:	Neutropenia, thrombocytopenia, anaemia
Common:	Pancytopenia, febrile neutropenia
Uncommon:	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare:	Haemolytic anaemia, thrombotic microangiopathy
Metabolism and nutrition disorders	
Common:	Anorexia
Uncommon:	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia

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

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

Rare:	Haemorrhagic corpus luteum/haemorrhagic ovarian cyst
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased
Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

* These types of reactions have been reported mainly from post-marketing experience with imatinib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to imatinib exposure.

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

2 Headache was the most common in GIST patients.

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

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

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

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

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

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

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

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

<u>*Laboratory test abnormalities*</u>

Haematology

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 109/l) and thrombocytopenias (platelet count < 50 x 109/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59–64% and 44–63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). In newly diagnosed chronic phase CML, grade 4 neutropenia (ANC < 0.5 x 109/l) and thrombocytopenia (platelet count < 10 x 109/l) were observed in 3.6% and < 1% of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with imatinib but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients, the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

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

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

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

<u>Description of selected adverse reactions</u>

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

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

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 9.4 Antineoplastic and immunosuppressive medicines: Miscellaneous cytotoxic agents.

Mechanism of action

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR- beta). Imatinib can also inhibit cellular events mediated by the activation of these receptor kinases.

Pharmacodynamic effects

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

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

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating kit mutation. Constitutive activation of the PDGF receptor or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.

Clinical studies in chronic myeloid leukaemia

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

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

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

Chronic phase newly diagnosed: This phase III study in adult patients compared treatment with either single-agent imatinib or a combination of interferon-alpha (IFN) plus cytarabine (Ara-C). Patients showing lack of response (lack of complete haematological response (CHR) at 6 months, increasing WBC, no major cytogenetic response (MCyR) at 24 months), loss of response (loss of CHR or MCyR) or severe intolerance to treatment were allowed to cross over to the alternative treatment arm. In the imatinib arm, patients were treated with 400 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m2/day for 10 days/month.

A total of 1,106 patients were randomised, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18–70 years), with 21.9% of patients ≥ 60 years of age. There were 59% males and 41% females; 89.9% caucasian and 4.7% black patients. Seven years after the last patient had been recruited, the median duration of first-line treatment was 82 and 8 months in the imatinib and IFN arms, respectively. The median duration of second-line treatment with imatinib was 64 months. Overall, in patients receiving first-line imatinib, the average daily dose delivered was 406± 76 mg. The primary efficacy endpoint of the study is progression-free survival. Progression was defined as any of the following events: progression to accelerated phase or blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. Major cytogenetic response, haematological response, molecular response (evaluation of minimal residual disease), time to accelerated phase or blast crisis and survival are the main secondary endpoints.

Response data is shown in Table 2.

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

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

* p<0.001, Fischer's exact test.
** molecular response percentages are based on available samples.
Haematological response criteria (all responses to be confirmed after ≥ 4 weeks): WBC < 10 x 109/l, platelet < 450 x 109/l, myelocyte+metamyelocyte < 5% in blood, no blasts and promyelocytes in blood, basophils < 20%, no extramedullary involvement.
Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1-35%), minor (36-65%) or minimal (66-95%). A major response (0-35%) combines both complete and partial responses.
Major molecular response criteria: in the peripheral blood reduction of ≥ 3 logarithms in the amount of Bcr-Abl transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardised baseline.

Rates of complete haematological response, major cytogenetic response and complete cytogenetic response on first-line treatment were estimated using the Kaplan-Meier approach, for which non-responses were censored at the date of last examination. Using this approach, the estimated cumulative response rates for first-line treatment with imatinib improved from 12 months of therapy to 84 months of therapy as follows: CHR from 96.4% to 98.4% and CCyR from 69.5% to 87.2%, respectively.

With 7 years follow-up, there were 93 (16.8%) progression events in the imatinib arm: 37 (6.7%) involving progression to accelerated phase/blast crisis, 31 (5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in WBC, and 10 (1.8%) CML unrelated deaths. In contrast, there were 165 (29.8%) events in the IFN+Ara-C arm, of which 130 occurred during first- line treatment with IFN+Ara-C.

The estimated rate of patients free of progression to accelerated phase or blast crisis at 84 months was significantly higher in the imatinib arm compared to the IFN arm (92.5% versus 85.1%, $p<0.001$). The annual rate of progression to accelerated phase or blast crisis decreased with time on therapy and was less than 1% annually in the fourth and fifth years. The estimated rate of progression-free survival at 84 months was 81.2% in the imatinib arm and 60.6% in the control arm ($p<0.001$). The yearly rates of progression of any type for imatinib also decreased over time.

A total of 71 (12.8%) and 85 (15.4%) patients died in the imatinib and IFN+Ara-C groups, respectively. At 84 months, the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80,87) in the randomised imatinib and the IFN+Ara-C groups, respectively ($p=0.073$, log-rank test). This time-to-event endpoint is strongly affected by the high crossover rate from IFN+Ara-C to imatinib. The effect of imatinib treatment on survival in chronic phase, newly diagnosed CML has been further examined in a retrospective analysis of the above reported imatinib data with the primary data from another Phase III study using IFN+Ara- C (n=325) in an identical regimen. In this retrospective analysis, the superiority of imatinib over IFN+Ara-C in overall survival was demonstrated ($p<0.001$); within 42 months, 47 (8.5%) imatinib patients and 63 (19.4%) IFN+Ara-C patients had died.

The degree of cytogenetic response and molecular response had a clear effect on long-term outcomes in patients on imatinib. Whereas an estimated 96% (93%) of patients with CCyR (PCyR) at 12 months were free of progression to accelerated phase/blast crisis at 84 months, only 81% of patients without MCyR at 12 months were free of progression to advanced CML at 84 months ($p<0.001$ overall, $p=0.25$ between CCyR and PCyR). For patients with reduction in Bcr-Abl transcripts of at least 3 logarithms at 12 months, the probability of remaining free from progression to accelerated phase/blast crisis was 99% at 84 months. Similar findings were found based on an 18-months landmark analysis.

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

Chronic phase Interferon failure
532 adult patients were treated at a starting dose of 400 mg. The patients were distributed in three main categories: haematological failure (29%), cytogenetic failure (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥ 25 x 106 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. The primary efficacy variable of the study was the rate of major cytogenetic response (complete plus partial response, 0 to 35% Ph+ metaphases in the bone marrow).

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

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

The primary efficacy variable was the rate of haematological response, reported as either complete haematological response, no evidence of leukaemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. A confirmed haematological response was achieved in 71.5% of patients (Table 3).

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

Myeloid blast crisis
260 patients with myeloid blast crisis were enrolled. 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg, the protocol was subsequently amended to allow higher dosing and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the rate of haematological response, reported as either complete haematological response, no evidence of leukaemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. In this study, 31% of patients achieved a haematological response (36% in previously untreated patients and 22% in previously treated patients). The rate of response was also higher in the patients treated at 600 mg (33%) as compared to the patients treated at 400 mg (16%, p=0.0220). The current estimate of the median survival of the previously untreated and treated patients was 7.7 and 4.7 months, respectively.

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

Table 3 Response in adult CML studies

	Study 0110 37-month data Chronic phase, IFN failure (n=532)	Study 0109 40.5-month data Accelerated phase (n=235)	Study 0102 38-month data Myeloid blast crisis (n=260)
% of patients ($CI_{95\%}$)			
Haematological response[1]	95% (92.3–96.3)	71% (65.3–77.2)	31% (25.2–36.8)
Complete haematological response (CHR)	95%	42%	8%
No evidence of leukaemia (NEL)	Not applicable	12%	5%
Return to chronic phase (RTC)	Not applicable	17%	18%
Major cytogenetic response[2]	65% (61.2–69.5)	28% (22.0–33.9)	15% (11.2–20.4)
Complete (Confirmed[3]) [95% CI]	53% (43%) [38.6–47.2]	20% (16%) [11.3–21.0]	7% (2%) [0.6–4.4]
Partial	12%	7%	8%

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

CHR: Study 0110 [WBC < 10 x 10^9/l, platelets < 450 x 10^9/l, myelocyte+metamyelocyte < 5% in blood, no blasts and promyelocytes in blood, basophils < 20%, no extramedullary involvement] and in studies 0102 and 0109 [ANC ≥ 1.5 x 10^9/l, platelets ≥ 100 x 10^9/l, no blood blasts, BM blasts < 5% and no extramedullary disease]

NEL Same criteria as for CHR but ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l (0102 and 0109 only)

RTC < 15% blasts BM and PB, < 30% blasts+promyelocytes in BM and PB, < 20% basophils in PB, no extramedullary disease other than spleen and liver (only for 0102 and 0109)

BM = bone marrow, PB = peripheral blood

[2] **Cytogenetic response criteria:**

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

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

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

A total of 51 paediatric patients with newly diagnosed and untreated CML in chronic phase have been enrolled in an open-label, multicentre, single-arm phase II trial. Patients were treated with imatinib 340 mg/m2/day, with no interruptions in the absence of dose limiting toxicity. Imatinib treatment induces a rapid response in newly diagnosed paediatric CML patients with a CHR of 78% after 8 weeks of therapy. The high rate of CHR is accompanied by the development of a complete cytogenetic response (CCyR) of 65% which is comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16% for a MCyR of 81%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10, with a median time to response based on the Kaplan-Meier estimate of 5.6 months.

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

<u>Clinical studies in Ph+ ALL</u>

Newly diagnosed Ph+ ALL
In a controlled study (ADE10) of imatinib versus chemotherapy induction in 55 newly diagnosed patients aged 55 years and over, imatinib used as single agent induced a significantly higher rate of complete haematological response than chemotherapy (96.3% vs. 50%; p=0.0001). When salvage therapy with imatinib was administered to patients who did not respond or who responded poorly to chemotherapy, it resulted in 9 patients (81.8%) out of 11 achieving a complete haematological response. This clinical effect was associated with a higher reduction in bcr- abl transcripts in the imatinib-treated patients than in the chemotherapy arm after 2 weeks of therapy (p=0.02).

All patients received imatinib and consolidation chemotherapy (see Table 4) after induction and the levels of bcr-abl transcripts were identical in the two arms at 8 weeks. As expected on the basis of the study design, no difference was observed in remission duration, disease-free survival or overall survival, although patients with complete molecular response and remaining in minimal residual disease had a better outcome in terms of both remission duration (p=0.01) and disease-free survival (p=0.02).

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

Table 4 Chemotherapy regimen used in combination with imatinib

Study ADE10	
Prephase	DEX 10 mg/m2 oral, days 1-5; CP 200 mg/m2 i.v., 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 i.v., days 7, 14; IDA 8 mg/m2 i.v. (0.5 h), days 7, 8, 14, 15; CP 500 mg/m2 i.v.(1 h) day 1; Ara-C 60 mg/m2 i.v., days 22-25, 29-32
Consolidation therapy I, III, V	MTX 500 mg/m2 i.v. (24 h), days 1, 15; 6-MP 25 mg/m2 oral, days 1-20
Consolidation therapy II, IV	Ara-C 75 mg/m2 i.v. (1 h), days 1-5; VM26 60 mg/m2 i.v. (1 h), days 1-5
Study AAU02	
Induction therapy (*de novo* Ph+ ALL)	Daunorubicin 30 mg/m2 i.v., days 1-3, 15-16; VCR 2 mg total dose i.v., days 1, 8, 15, 22; CP 750 mg/m2 i.v., 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 1,000 mg/m2/12 h i.v.(3 h), days 1-4; Mitoxantrone 10 mg/m2 i.v. days 3-5; MTX 15 mg intrathecal, day 1; Methylprednisolone 40 mg intrathecal, day 1
Study ADE04	
Prephase	DEX 10 mg/m2 oral, days 1-5; CP 200 mg/m2 i.v., days 3-5;
	MTX 15 mg intrathecal, day 1
Consolidation (*de novo* Ph+ ALL)	Ara-C 1,000 mg/m2/12 h i.v.(3 h), days 1-4; Mitoxantrone 10 mg/m2 i.v. days 3-5; MTX 15 mg intrathecal, day 1; Methylprednisolone 40 mg intrathecal, day 1
Study ADE04	
Prephase	DEX 10 mg/m2 oral, days 1-5; CP 200 mg/m2 i.v., days 3-5; MTX 15 mg intrathecal, day 1

Induction therapy I	DEX 10 mg/m2 oral, days 1-5; VCR 2 mg i.v., days 6, 13, 20; Daunorubicin 45 mg/m2 i.v., days 6-7, 13-14
Induction therapy II	CP 1 g/m2 i.v. (1 h), days 26, 46; Ara-C 75 mg/m2 i.v. (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 i.v., day 1; MTX 1.5 g/m2 i.v. (24 h), day 1; Etoposide 250 mg/m2 i.v. (1 h) days 4-5; Ara-C 2x 2 g/m2 i.v. (3 h, q 12 h), day 5
Study AJP01	
Induction therapy	CP 1.2 g/m2 i.v. (3 h), day 1; Daunorubicin 60 mg/m2 i.v. (1 h), days 1-3; Vincristine 1.3 mg/m2 i.v., days 1, 8, 15, 21; Prednisolone 60 mg/m2/day oral
Consolidation therapy	Alternating chemotherapy course: high dose chemotherapy with MTX 1 g/m2 i.v. (24 h), day 1, and Ara-C 2 g/m2 i.v. (q 12 h), days 2-3, for 4 cycles
Maintenance	VCR 1.3 g/m2 i.v., day 1; Prednisolone 60 mg/m2 oral, days 1-5
Study AUS01	
Induction-consolidation therapy	Hyper-CVAD regimen: CP 300 mg/m2 i.v. (3 h, q 12 h), days 1-3; Vincristine 2 mg i.v., days 4, 11; Doxorubicine 50 mg/m2 i.v. (24 h), day 4; DEX 40 mg/day on days 1-4 and 11-14, alternated with MTX 1 g/m2 i.v. (24 h), day 1, Ara-C 1 g/m2 i.v. (2 h, q 12 h), days 2-3 (total of 8 courses)
Maintenance	VCR 2 mg i.v. monthly for 13 months; Prednisolone 200 mg oral, 5 days per month for 13 months
All treatment regimens include administration of steroids for CNS prophylaxis.	
Ara-C: cytosine arabinoside; CP: cyclophosphamide; DEX: dexamethasone; MTX: methotrexate; 6-MP: 6-mercaptopurine VM26: Teniposide; VCR: vincristine; IDA: idarubicine; i.v.: intravenous	

Paediatric patients

In study I2301, a total of 93 paediatric, adolescent and young adult patients (from 1 to 22 years old) with Ph+ ALL were enrolled in an open-label, multicentre, sequential cohort, non-randomised phase III trial, and were treated with imatinib (340 mg/m2/day) in combination with intensive chemotherapy after induction therapy. Imatinib was administered intermittently in cohorts 1-5, with increasing duration and earlier start of imatinib from cohort to cohort; cohort 1 receiving the lowest intensity and cohort 5 receiving the highest intensity of imatinib (longest duration in days with continuous daily imatinib dosing during the first chemotherapy treatment courses). Continuous daily exposure to imatinib early in the course of treatment in combination with chemotherapy in cohort 5-patients (n=50) improved the 4-year event-free survival (EFS) compared to historical controls (n=120), who received standard chemotherapy without imatinib (69.6% vs. 31.6%, respectively). The estimated 4-year OS in cohort 5-patients was 83.6% compared to 44.8% in the historical controls. 20 out of the 50 (40%) patients in cohort 5 received haematopoietic stem cell transplant.

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

Consolidation block 1 (3 weeks)	VP-16 (100 mg/m2/day, IV): days 1-5 Ifosfamide (1.8 g/m2/day, IV): days 1-5 MESNA (360 mg/m2/dose q3h, x 8 doses/day, IV): days 1-5 G-CSF (5 µg/kg, SC): days 6-15 or until ANC > 1500 post nadir IT Methotrexate (age-adjusted): day 1 ONLY Triple IT therapy (age-adjusted): day 8, 15
Consolidation block 2 (3 weeks)	Methotrexate (5 g/m2 over 24 hours, IV): day 1 Leucovorin (75 mg/m2 at hour 36, IV; 15 mg/m2 IV or PO q6h x 6 doses)iii: Days 2 and 3 Triple IT therapy (age-adjusted): day 1 ARA-C (3 g/m2/dose q 12 h x 4, IV): days 2 and 3 G-CSF (5 µg/kg, SC): days 4-13 or until ANC > 1500 post nadir
Reinduction block 1 (3 weeks)	VCR (1.5 mg/m2/day, IV): days 1, 8, and 15 DAUN (45 mg/m2/day bolus, IV): days 1 and 2 CPM (250 mg/m2/dose q12h x 4 doses, IV): days 3 and 4 PEG-ASP (2500 IUnits/m2, IM): day 4 G-CSF (5 µg/kg, SC): days 5-14 or until ANC > 1500 post nadir Triple IT therapy (age-adjusted): days 1 and 15 DEX (6 mg/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 hour 36, IV; 15 mg/m2 IV or PO q6h x 6 doses)iii: Days 2, 3, 16, and 17 Triple IT therapy (age-adjusted): days 1 and 22 VP-16 (100 mg/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 µg/kg, SC): days 27-36 or until ANC > 1500 post nadir ARA-C (3 g/m2, q12h, IV): days 43, 44 L-ASP (6000 IUnits/m2, IM): day 44

Reinduction 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 q12h x 4 doses, iv): Days 3 and 4 PEG-ASP (2500 IUnits/m2, IM): day 4 G-CSF (5 µg/kg, SC): days 5-14 or until ANC > 1500 post nadir Triple IT therapy (age-adjusted): days 1 and 15 DEX (6 mg/m2/day, PO): days 1-7 and 15-21
Intensification block 2 (9 weeks)	Methotrexate (5 g/m2 over 24 hours, IV): days 1 and 15 Leucovorin (75 mg/m2 at hour 36, IV; 15 mg/m2 IV or PO q6h x 6 doses)iii: days 2, 3, 16, and 17 Triple IT therapy (age-adjusted): days 1 and 22 VP-16 (100 mg/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 µg/kg, SC): days 27-36 or until ANC > 1500 post nadir ARA-C (3 g/m2, q12h, IV): days 43, 44 L-ASP (6000 IUnits/m2, IM): day 44
Maintenance (8-week cycles) Cycles 1–4	MTX (5 g/m2 over 24 hours, IV): day 1 Leucovorin (75 mg/m2 at hour 36, IV; 15 mg/m2 IV or PO q6h x 6 doses)iii: days 2 and 3 Triple IT therapy (age-adjusted): days 1, 29 VCR (1.5 mg/m2, IV): days 1, 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, 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 µg/kg, SC): days 34-43
Maintenance (8-week cycles) Cycle 5	Cranial irradiation (Block 5 only) 12 Gy in 8 fractions for all patients that are CNS1 and CNS2 at diagnosis 18 Gy in 10 fractions for patients that are CNS3 at diagnosis VCR (1.5 mg/m2/day, IV): days 1, 29 DEX (6 mg/m2/day, PO): days 1-5; 29-33 6-MP (75 mg/m2/day, PO): days 11-56 (Withhold 6-MP during the 6-10 days of cranial irradiation beginning on day 1 of Cycle 5. Start 6-MP the 1st day after cranial irradiation completion.) Methotrexate (20 mg/m2/week, PO): days 8, 15, 22, 29, 36, 43, 50
Maintenance (8-week cycles) Cycles 6-12	VCR (1.5 mg/m2/day, IV): days 1, 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, 50

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

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

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

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

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

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

There are no controlled trials in paediatric patients with MDS/MPD. Five (5) patients with MDS/MPD associated with PDGFR gene re-arrangements were reported in 4 publications. The age of these patients ranged from 3 months to 4 years and imatinib was given at dose 50 mg daily or doses ranging from 92.5 to 340 mg/m2 daily. All patients achieved a complete haematological response, cytogenetic response and/or clinical response.

Clinical studies in HES/CEL

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

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

Clinical studies in DFSP

One phase II, open label, multicentre clinical trial (study B2225) was conducted, including 12 patients with DFSP treated with imatinib 800 mg daily. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial resective surgery and not considered amenable to further resective surgery at the time of study entry. The primary evidence of efficacy was based on objective response rates. Out of the 12 patients enrolled, 9 responded, one completely and 8 partially. Three of the partial responders were subsequently rendered disease free by surgery. The median duration of therapy in study B2225 was 6.2 months, with a maximum duration of 24.3 months. A further 6 DFSP patients treated with imatinib were reported in 5 published case reports, their ages ranging from 18 months to 49 years. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) imatinib daily. Five (5) patients responded, 3 completely and 2 partially. The median duration of therapy in the published literature ranged between 4 weeks and more than 20 months. The translocation t(17:22)[(q22:q13)], or its gene product, was present in nearly all responders to imatinib treatment.

There are no controlled trials in paediatric patients with DFSP. Five (5) patients with DFSP and PDGFR gene re-arrangements were reported in 3 publications. The age of these patients ranged from newborn to 14 years and imatinib was given at dose 50 mg daily or doses ranging from 400 to 520 mg/m2 daily. All patients achieved partial and/or complete response.

5.2 Pharmacokinetic properties

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

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

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

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

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

The *in vitro* results showed that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin (IC_{50} 50 µM) and fluconazole (IC50 118 µM) showed inhibition of imatinib metabolism which could have clinical relevance.

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

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

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

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

Pharmacokinetics in children
As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m2/day achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on day 8 and day 1 at the 340 mg/m^2/day dose level revealed a 1.7-fold drug accumulation after repeated once-daily dosing.

Based on pooled population pharmacokinetic analysis in paediatric patients with haematological disorders (CML, Ph+ALL, or other haematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in paediatric patients receiving 260 mg/m2 once daily (not exceeding 400 mg once daily) or 340 mg/m2 once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

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

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

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

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

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

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

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

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤ 20 mg/kg. A slight to moderate reduction in spermatogenesis was also observed in the dog at oral doses ≥ 30 mg/kg. When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on the number of pregnant females. At a dose of 60 mg/kg, female rats had significant post-implantation foetal loss and a reduced number of live foetuses. This was not seen at doses ≤ 20 mg/kg.

In an oral pre- and postnatal development study in rats, red vaginal discharge was noted in the 45 mg/kg/day group on either day 14 or day 15 of gestation. At the same dose, the number of stillborn puppies as well as those dying between postpartum days 0 and 4 was increased. In the F1 offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. F1 fertility was not affected, while an increased number of resorptions and a decreased number of viable foetuses was noted at 45 mg/kg/day. The no observed effect level (NOEL) for both the maternal animals and the F1 generation was 15 mg/kg/day (one quarter of the maximum human dose of 800 mg).

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

No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 postpartum) with respect to the known target organs in adult rats. In the juvenile toxicology study, effects upon growth, delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m2. In addition, mortality was observed in juvenile animals (around the weaning phase) at approximately 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m2.

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

Papilloma/carcinoma of the preputial/clitoral gland were noted from 30 mg/kg/day onwards, representing approximately 0.5 or 0.3 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 15 mg/kg/day. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day, representing approximately 1.7 or 1 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 1.2 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 30 mg/kg/day.

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

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

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

6. Pharmacological particulars

6.1 List of excipients

Core
Microcrystalline cellulose
Low substituted hydroxypropyl cellulose
Povidone
Crospovidone
Silica colloidal anhydrous
Magnesium stearate

Coating
Hypromellose
Macrogol 400
Talc
Red Iron oxide
Yellow Iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The tablets are packed in PVC/PE/PVDC/Aluminium blisters.

<u>Imarem 100</u>
Pack size of 6x10 film-coated tablets.

<u>Imarem 400</u>
Pack size of 3x10 film-coated tablets.

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. APPLICANT
Remedica Limited
Aharnon Street, Limassol Industrial Estate
3056 Limassol
Cyprus

8. MANUFACTURER
Remedica Limited
Aharnon Street, Limassol Industrial Estate
3056 Limassol
Cyprus

9. REGISTRATION DETAILS
<u>Imarem 100</u>
Zimbabwe registration number: 2023/9.4/6408
Zimbabwe category for distribution: Prescription Preparations (P.P.)

<u>Imarem 400</u>
Zimbabwe registration number: 2023/9.4/6409
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT
July 2023