TYKONIB
(Imatinib Mesylate Tablets 100mg/400mg)

1. NAME OF MEDICINAL PRODUCT
Tykonib 100 (Imatinib Mesylate Tablets 100 mg)
Tykonib 400 (Imatinib Mesylate Tablets 400 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tykonib 100 : Each film coated tablet contains: Imatinib Mesylate 119.50 mg equivalent to Imatinib 100 mg
Tykonib 400 : Each film coated tablet contains: Imatinib Mesylate 478 mg equivalent to
Imatinib 400 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tykonib 100
Very dark yellow to brownish orange, film-coated tablets, round, biconvex with beveled edges, debossed with "IMT" on one side and score on other side

Tykonib 400
Very dark yellow to brownish orange, film-coated tablets, oval, biconvex with beveled edges, debossed with "400" on one side and "IMT" on other side

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

The effect of Imatinib on the outcome of bone marrow transplantation has not been determined.
Imatinib film-coated tablets is indicated for
- 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 film-coated tablets 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 film-coated tablets in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.
For doses other than 400 mg and 800 mg (see dosage recommendation below) a 100 mg divisible tablet is available.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal irritations. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.
For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of still water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Posology for CML in adult patients
The recommended dosage of imatinib is 400 mg/day for adult patients in chronic phase CML. Chronic phase CML is defined when all of the following criteria are met: blasts < 15% in blood and bone marrow, peripheral blood basophils < 20%, platelets > 100 x 109/l.
The recommended dosage of imatinib is 600 mg/day for adult patients in accelerated phase. Accelerated phase is defined by the presence of any of the following: blasts ≥ 15% but < 30% in blood or bone marrow, blasts plus promyelocytes ≥ 30% in blood or bone marrow (providing < 30% blasts), peripheral blood basophils ≥ 20%, platelets < 100 x 109/l unrelated to therapy.
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: In clinical trials, treatment with imatinib was continued until disease progression. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.
Dose increases from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients with accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for CML in children
Dosing for children should be on the basis of body surface area (mg/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 in adult patients
The recommended dose of 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 Ph+ ALL 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 Ph+ ALL (not to exceed the total dose of 600 mg).

Posology for MDS/MPD
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.

Dose adjustment for adverse reactions
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/m²)	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/m².
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of 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/m²)	[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/m². 3. If cytopenia persists for 2 weeks, reduce further to 200 mg/m². 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/m².
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 and with Ph+ALL below 1 year 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 have not been established in clinical trials. Currently available published data are summarised in section 5.1 but no recommendation on a posology can be made.
Hepatic insufficiency: Imatinib is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections 4.4, 4.8 and 5.2).
Liver dysfunction classification

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

ULN = upper limit of normal for the institution
AST = aspartate aminotransferase
Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see sections 4.4 and 5.2).
Older people: Imatinib pharmacokinetics have not been specifically studied in older people. No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in older people.

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

4.4 Special warnings and precautions for use
When 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, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives (see section 4.5).
Concomitant use of imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to 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). It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.
Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.5 and 4.8).

Fluid retention
Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking 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
In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra- tumoural haemorrhages were reported (see section 4.8). Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.
In addition, gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of 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).

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

Thrombotic microangiopathy
BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for imatinib (see section 4.8). If laboratory or clinical 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.

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. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

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 Cmax 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. Pretreatment 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–∞) 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 Cmax 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-administered with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.
In vitro, imatinib inhibits 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 Fertility, pregnancy and lactation
Women of childbearing potential
Women of childbearing potential must be advised to use effective contraception during treatment.

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

Breast-feeding
There is limited information on imatinib distribution on human milk. Studies in two breast-feeding women revealed that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women 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 the study drug was discontinued for drug-related adverse reactions in 4% of patients.
The adverse reactions were similar in all indications, with two exceptions. There was more myelosuppression seen in CML patients than in GIST, which is probably due to the underlying disease. In the study in patients with unresectable and/or metastatic GIST, 7 (5%) patients experienced CTC grade 3/4 GI bleeds (3 patients), intra-tumoural bleeds (3 patients) or both (1 patient). GI tumour sites may have been the source of the GI bleeds (see section 4.4). GI and tumoural bleeding may be serious and sometimes fatal. The most commonly reported (≥ 10%) drug- related adverse reactions in both settings were mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of 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 common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Not known:	Ileus/intestinal obstruction*, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (GAVE)*
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[8], hepatic necrosis
Skin and subcutaneous tissue disorders	
Very common:	Periorbital oedema, dermatitis/eczema/rash
Common:	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions
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:	Avascular 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.

Laboratory test abnormalities
Haematology
In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg (phase I study).
However, the occurrence of cytopenias was also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 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.

Description of selected adverse reactions

Hepatitis B reactivation

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at Website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: protein-tyrosine kinase inhibitor, ATC code: L01XE01

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

Pharmacodynamic effects
Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular and in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.
In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. 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 main secondary endpoints. Response data are shown in Table 2.

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

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

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 seem to be in line with the safety profile of imatinib in Ph+ ALL patients.

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

Clinical studies in MDS/MPD

Experience with 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 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/m2 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 Cmax and prolongation of tmax 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(0-48h)). 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 (IC50 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. Ki values in human liver microsomes were 27, 7.5 and 7.9 µmol/l, respectively. Maximal plasma concentrations of imatinib in patients are 2–4 µmol/l, consequently an inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil, but it inhibited paclitaxel metabolism as a result of competitive inhibition of CYP2C8 (Ki = 34.7 µM). This Ki value is far higher than the expected plasma levels of imatinib in patients, consequently no interaction is expected upon co- administration of either 5-fluorouracil or paclitaxel and imatinib.

Elimination

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 t½ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25–1,000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5–2.5-fold at steady state when dosed once daily.

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/m2/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 number of pregnant females. At a dose of 60 mg/kg, female rats had significant post- implantation foetal loss and a reduced number of live foetuses. This was not seen at doses ≤ 20 mg/kg.

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

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

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