

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Imatinib 100 mg Film Coated Tablets

Imatinib 400 mg Film Coated Tablets

Imatinib mesilate 100 / 400 mg

COMPOSITION

Imatinib mesilate 100 mg

Each film coated tablet contains imatinib mesilate equivalent to imatinib 100 mg.

Imatinib mesilate 400 mg

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

DOSAGE FORM

Film Coated Tablet

PRODUCT DESCRIPTION

Imatinib mesilate 100 mg, divisible

Very dark yellow to brownish orange, film coated tablets, round, biconvex with bevelled edges, debossed with "C211" on one side with score on other side.

Imatinib mesilate 400 mg, divisible

Very dark yellow to brownish orange, film coated tablets, Ovaloid, biconvex with bevelled edges, debossed with "C212" on one side with score on other side.

The tablet can be divided into equal doses.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: protein-tyrosine kinase inhibitor, ATC code: L01EA01

Mechanism of action

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

Pharmacodynamic effects

Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the breakpoint cluster region-Abelson (Bcr-Abl) tyrosine kinase at the *in vitro*, cellular 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 colony transformation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients.

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

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), and stem cell factor (SCF), KIT, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating *kit* mutation. Constitutive activation of the PDGF receptor or the ABL protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of KIT or the PDGFR has been implicated in the pathogenesis of ASM. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, KIT and ABL kinase activity.

Pharmacokinetics

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

Distribution

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

Biotransformation/metabolism

The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP71588), which shows similar *in vitro* potency as the parent compound. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Elimination

Based on the recovery of compound(s) after an oral ^{14}C -labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in faeces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% faeces), the remainder being metabolites. The mean apparent elimination half-life estimated from the single dose PK study was 13.5 hours. The half-life of all ^{14}C -labelled components in plasma was from 41-72 hours.

Plasma pharmacokinetics

Following oral administration, the $t_{1/2}$ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 to 1,000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5 to 2.5 fold at steady state when dosed once daily.

Special Populations

Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant. The effect of 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.

Paediatric Patients (below 18 years)

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients. Dosing in children at 260 and 340 mg/m² 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 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.

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.

INDICATIONS

Imatib is indicated for the treatment of

- adult and paediatric patients with newly diagnosed chronic myeloid leukaemia (CML) as well as for the treatment of adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- adult patients with unresectable and / or metastatic malignant gastrointestinal stromal tumours (GIST).
- adjuvant treatment of adult patients following resection of GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- 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 hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFR α rearrangement.
- adult patients with unresectable, recurrent and / or metastatic dermatofibrosarcoma protuberans (DFSP).
- adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.

The effectiveness of Imatib 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 ASM and on objective response rates

in GIST and DFSP, and on recurrence-free survival in adjuvant GIST. The experience with Imatib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival in diseases.

DOSAGE 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 disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.

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

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

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

Posology

Dosage in CML

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

Dose increase 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 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.

See section on special populations for pediatric patients.

Dosage in Ph+ ALL

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

Dosage in MDS / MPD

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

Dosage in ASM

The recommended dose of imatinib is 400 mg/day for adult patients with ASM without the D816V c-KIT mutation or mutational status unknown or not responding satisfactorily to other therapies.

For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR- α , a starting dose of 100 mg/day is recommended. A dose increase

from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL

The recommended dose of imatinib is 400 mg/day for adult patients with HES/CEL.

For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha fusion kinase, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in GIST

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

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

The recommended dose of imatinib is 400 mg / day for the adjuvant treatment of adult patients following complete gross resection of GIST. The optimal treatment duration with imatinib is not known.

Dosage in 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 $> 3 \times$ institutional upper limit of normal (IULN) or in liver transaminases $> 5 \times$ IULN occur, imatinib should be withheld until bilirubin levels have returned to $< 1.5 \times$ IULN and transaminase levels to $< 2.5 \times$ 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:

ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC $< 1.0 \times 10^9/l$ and/or platelets $< 50 \times 10^9/l$	1. Stop imatinib until ANC $\geq 1.5 \times 10^9/l$ and platelets $\geq 75 \times 10^9/l$. 2. Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD, ASM, HES/CEL and GIST (starting dose 400 mg)	ANC $< 1.0 \times 10^9/l$ and/or platelets $< 50 \times 10^9/l$	1. Stop imatinib until ANC $\geq 1.5 \times 10^9/l$ and platelets $\geq 75 \times 10^9/l$. 2. Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC $< 1.0 \times 10^9/l$ and/or platelets $< 50 \times 10^9/l$, 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 .
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg ^c)	^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 ^b . 3. If cytopenia persists for 2 weeks, reduce further to 300 mg ^d . 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 ^d .
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 ^b or 260 mg/m ² in pediatric patients ^c or 340 mg/m ² in pediatric patients ^d or 200 mg/m ² in pediatric patients		

Special populations

Renal insufficiency

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

Hepatic impairment

Imatinib is mainly metabolised by the liver. Patients with mild, moderate or severe liver impairment should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.

Paediatric patient (below 18 years)

There is no experience with the use of imatinib in paediatric patients with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited to no experience with the use of imatinib in paediatric patients in other indications.

Dosing in paediatric patients 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 and advanced phase CML and Ph+ ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening.

Geriatric patients (65 years or above)

No significant age-related pharmacokinetic differences have been observed in adult patients. No specific dose recommendation is necessary in older people.

CONTRAINDICATIONS

Use in patients with a hypersensitivity to the active substance or to any of the excipients is contraindicated.

WARNINGS AND PRECAUTIONS

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

Hypothyroidism

Hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Hepatotoxicity

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

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

Fluid retention

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

Patients with cardiac disease or renal failure

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

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Myelodysplastic (MDS) / myeloproliferative diseases (MPD) and systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

Gastrointestinal haemorrhages and tumor haemorrhages have been reported in patients with unresectable or metastatic malignant GIST. The tumour haemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumor lesions. GI sites of tumor may have contributed to GI bleeding in this reported patient population.

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. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with imatinib. When needed, imatinib discontinuation may be considered.

Tumour lysis syndrome

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

Hepatitis B reactivation

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

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

Laboratory tests

Haematology

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

Liver Function

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

Renal Function

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics. In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. There is no correlation between imatinib exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCL), between patients with mild (CrCL: 40 to 59 mL/min) and severe (CrCL: <20 mL/min) renal impairment. However, as recommended in section Dosage and Method of Administration the starting dose of imatinib can be reduced if not tolerated.

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

Paediatric patients (below 18 years)

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

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for Imatinib. 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 antiADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Imatinib should not be resumed.

INTERACTIONS WITH OTHER MEDICAMENTS

Observed interactions resulting in a concomitant use not recommended

Drugs that may **decrease** imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to imatinib. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Other interactions that may affect exposure to imatinib or other drugs

Drugs that may **increase** imatinib plasma concentrations:

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase imatinib concentrations. Caution should be taken when administering imatinib with inhibitors of the CYP3A4 family.

Drugs that may have their plasma concentration altered by imatinib

Imatinib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2 and 3.5 fold, respectively, indicating an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

Imatinib also inhibits CYP2C9 and CYP2C19 activity *in vitro*. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of imatinib therapy and when altering the dosage. Alternatively, the use of low-molecular-weight heparin should be considered.

In vitro, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by

approximately 23%. Co-administration of imatinib with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.

In vitro, imatinib inhibits the acetaminophen O-glucuronidate pathway (K_i 58.5 μ M).

Co-administration of imatinib (400 mg/day for eight days) with acetaminophen/paracetamol (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen/paracetamol.

Imatinib pharmacokinetics was not altered in the presence of single-dose acetaminophen / paracetamol. There is no PK or safety data on the concomitant use of imatinib at doses > 400 mg /day or the chronic use of concomitant acetaminophen / paracetamol and imatinib.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Females

Females of reproductive potential should be advised to use effective contraception when using imatinib during treatment and for at least 15 days after stopping treatment with imatinib.

Pregnancy

Imatinib can cause fetal harm when administered to a pregnant woman based on findings from animal reproduction studies. There are no clinical trials 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. Imatinib should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Lactation

Both imatinib and its active metabolite can be transferred into human milk. The effects of low-dose exposure of the infant to imatinib are unknown, because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 15 days after stopping treatment with imatinib.

Fertility

Male patients concerned about their fertility on imatinib treatment should consult with their physician.

ADVERSE REACTIONS

Adverse reactions are reported by system organ class and by frequency. Frequency categories are defined using the following convention: very common, common, uncommon, rare, very rare, not known. Adverse reactions and their frequencies are reported in Table 1 and Table 2.

Table 1 Adverse drug reactions in clinical studies for CML and GIST

Infections and infestations	
<i>Uncommon:</i>	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia ¹ , sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
<i>Rare:</i>	Fungal infection
Blood and lymphatic system disorders	
<i>Very common:</i>	Neutropenia, thrombocytopenia, anaemia
<i>Common:</i>	Pancytopenia, febrile neutropenia

<i>Uncommon:</i>	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
<i>Rare:</i>	Haemolytic anaemia, Thrombotic microangiopathy
Metabolism and nutrition disorders	
<i>Common:</i>	Anorexia
<i>Uncommon:</i>	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
<i>Rare:</i>	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
<i>Common:</i>	Insomnia
<i>Uncommon:</i>	Depression, libido decreased, anxiety
<i>Rare:</i>	Confusional state
Nervous system disorders	
<i>Very common:</i>	Headache
<i>Common:</i>	Dizziness, paraesthesia, taste disturbance, hypoaesthesia
<i>Uncommon:</i>	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage
<i>Rare:</i>	Increased intracranial pressure, convulsions, optic neuritis
Eye disorders	
<i>Common:</i>	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision
<i>Uncommon:</i>	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
<i>Rare:</i>	Cataract, glaucoma, papilloedema
Ear and labyrinth disorders	
<i>Uncommon:</i>	Vertigo, tinnitus, hearing loss
Cardiac disorders	
<i>Uncommon:</i>	Palpitations, tachycardia, cardiac failure congestive, pulmonary oedema
<i>Rare:</i>	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Vascular disorders	
<i>Common:</i>	Flushing, haemorrhage
<i>Uncommon:</i>	Hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
<i>Common:</i>	Dyspnoea, epistaxis, cough
<i>Uncommon:</i>	Pleural effusion, pharyngolaryngeal pain, pharyngitis
<i>Rare:</i>	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
<i>Very common:</i>	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
<i>Common:</i>	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis

<i>Uncommon:</i>	Stomatitis, mouth ulceration, gastrointestinal haemorrhage, eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
<i>Rare:</i>	Colitis, ileus, inflammatory bowel disease
Hepatobiliary disorders	
<i>Common:</i>	Increased hepatic enzymes
<i>Uncommon:</i>	Hyperbilirubinaemia, hepatitis, jaundice
<i>Rare:</i>	Hepatic failure, hepatic necrosis
Skin and subcutaneous tissue disorders	
<i>Very common:</i>	Periorbital oedema, dermatitis/eczema/rash
<i>Common:</i>	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
<i>Uncommon:</i>	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasia, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions Palmar-plantar erythrodysesthesia syndrome, lichenoid keratosis
<i>Rare:</i>	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
<i>Very common:</i>	Muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain
<i>Common:</i>	Joint swelling
<i>Uncommon:</i>	Joint and muscle stiffness
<i>Rare:</i>	Muscular weakness, arthritis
Renal and urinary disorders	
<i>Uncommon:</i>	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
<i>Uncommon:</i>	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
General disorders and administration site conditions	
<i>Very common:</i>	Fluid retention and oedema, fatigue
<i>Common:</i>	Weakness, pyrexia, anasarca, chills, rigors
<i>Uncommon:</i>	Chest pain, malaise
Investigations	
<i>Very common:</i>	Weight increased
<i>Common:</i>	Weight decreased
<i>Uncommon:</i>	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
<i>Rare:</i>	Blood amylase increased

Table 2 Adverse drug reactions from post-marketing reports

Infections and infestations	
Not known:	Hepatitis B reactivation
Nervous system disorders	
Uncommon:	Cerebral oedema
Eye disorders	
Rare:	Vitreous haemorrhage
Cardiac disorders	
Rare:	Pericarditis, cardiac tamponade
Vascular disorders	
Uncommon:	Thrombosis/embolism
Very rare:	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Acute respiratory failure, interstitial lung disease
Gastrointestinal disorders	
Uncommon:	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation
Rare:	Diverticulitis, gastric antral vascular ectasia (GAVE)
Skin and subcutaneous tissue disorders	
Uncommon:	Palmar-plantar erythrodysesthesia syndrome, panniculitis (including erythema nodosum)
Rare:	Lichenoid keratosis, lichen planus, pemphigus
Very rare:	Toxic epidermal necrolysis
Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)
Uncommon:	Osteonecrosis
Rare:	Rhabdomyolysis/myopathy
Not known:	Growth retardation in children
Reproductive disorders	
Very rare:	Haemorrhagic corpus luteum / haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour lysis syndrome

OVERDOSE

Experience with higher than therapeutic doses is limited. Isolated cases of imatinib overdosage have been reported spontaneously and in the literature. Generally, the reported outcome in these cases was

improvement or recovery. In the event of overdosage, the patient should be observed and appropriate symptomatic treatment should be given.

Adult overdose

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):

Nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

8 to 10 g (single dose):

Vomiting and gastrointestinal pain.

Paediatric overdose

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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.

INCOMPATIBILITY

Not applicable

STORAGE AND INSTRUCTION FOR USE

Store below 30°C.

Protect from moisture. Store in the original package.

SHELF LIFE

24 months

PACKAGING INFORMATION

HDPE container containing 30 tablets.

MANUFACTURED BY**CIPLA LTD.**

S-103 to S-105, S-107 to S-112,
L-138, L-147, L-147/1 to L-147/3 & L-147/A.
Verna Industrial Estate, Verna,
Goa, India.

PRODUCT REGISTRATION HOLDER**CIPLA MALAYSIA SDN BHD**

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