## Imatinib Tablets 100 mg and Imatinib Tablets 400 mg

**Product Name**
Imamed 100
Imatinib Mesylate Tablets 100 mg
Imamed 400
Imatinib Mesylate Tablets 400 mg

**Name and Strength of Active Substance(s)**
Imatinib Mesylate 100 mg
Each film coated tablet contains Imatinib Mesylate equivalent to Imatinib ...100 mg
Imatinib Mesylate 400 mg
Each film coated tablet contains Imatinib Mesylate equivalent to Imatinib ...400 mg

**Product Description**
Imatinib Mesylate Tablets 100 mg:
Dark yellow to brownish orange colored, film coated tablets, round, biconvex with bevelled edges debossed with 'S' and '1' on either side of break line on one side and plain on other side.

Imatinib Mesylate Tablets 400 mg:

Dark yellow to brownish orange colored, film coated tablets, capsule shaped, biconvex with bevelled edges debossed with 'S' and '2' on either side of break line on one side and plain on other side.

**Pharmacodynamics**
Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase at the in vitro, cellular, in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukemia (ALL) patients. In colony transformation assays using ex vivoperipheral 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 tumor (GIST) cells, which express an activating KIT mutation. Constitutive activation of the PDGFR 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 signaling and proliferation of cells driven by dysregulated PDGFR, KIT and ABL kinase activity.

**Pharmacokinetics**
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.

*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.

The mean apparent elimination half-life estimated from the single dose PK study was 13.5 hours. The half-life of all 14C-labelled components in plasma was from 41-72 hours.

*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.

*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 body weight 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.

Further population PK analysis in the phase III study in newly diagnosed CML patients showed that the effect of covariates and co-medications on both clearance and volume of distribution appears to be small and is not sufficiently pronounced to warrant dose adjustment.

*Pediatric patients (below 18 years)*

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

Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, Ph+ALL, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in pediatric patients receiving 260 mg/m$^2$ once daily (not exceeding 400 mg once daily) or 340 mg/m$^2$ once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

*Organ function impairment*

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2 fold, corresponding to a 1.5 fold elevation of plasma 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 RECOMMENDED DOSE, WARNINGS AND PRECAUTIONS AND PHARMACODYNAMICS).

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, WARNINGS AND PRECAUTIONS, SIDE EFFECTS, PHARMACODYNAMICS AND PHARMACOKINETICS).

**Indications**
- Imatinib is indicated for the treatment of adult and pediatric patients with newly diagnosed chronic myeloid leukemia (CML) as well as for the treatment of adult and pediatric 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 pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with F1P1L1-PDGFRα 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 Imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and ASM and on objective response rates in GIST and DFSP, and on recurrence-free survival in adjuvant GIST (see section PHARMACODYNAMICS). The experience with Imatinib 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.

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

The prescribed dose should be administered orally with a meal and a large glass of water to minimize 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 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).

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

Monitoring of response to Imatinib 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.

**General target population:**
**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 in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response.

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-alpha, 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. In clinical trials one year of Imatinib and three years of Imatinib were studied. In the patient population defined in a second open label phase III study (SSG XVIII/AIO), three years of Imatinib is recommended. 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 adjustments for adverse drug reactions**
**Non-hematological adverse drug reactions**
If a severe non-hematological adverse drug 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 a <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 pediatric patients from 340 to 260 mg/m$^2$/day.

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

**Table 1: Dose adjustments for neutropenia and thrombocytopenia**

| | | |
|---|---|---|
| ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg) | ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L | 1.Stop Imatinib until ANC ≥ 1.5 x10$^9$/L and platelets ≥ 75 x10$^9$/L.<br>2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction). |
| Chronic phase CML, MDS/MPD, ASM, HES/CEL and GIST (starting dose 400 mg) | ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L | 1. Stop Imatinib until ANC ≥ 1.5 x10$^9$/L and platelets ≥ 75 x10$^9$/L.<br>2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction).<br>3. In the event of recurrence of ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L, repeat step 1 and resume Imatinib at reduced dose of 300 mg. |
| Pediatric chronic phase CML (at dose 340 mg/m$^2$) | ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L | 1. Stop Imatinib until ANC ≥ 1.5 x10$^9$/L and platelets ≥ 75 x10$^9$/L.<br>2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction)<br>3. In the event of recurrence of ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/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 mgc) | [a]ANC < 0.5 x10$^9$/L and/or platelets < 10 x10$^9$/L | 1. Check whether cytopenia is related to leukemia (marrow aspirate or biopsy).<br>2. If cytopenia is unrelated to leukemia, reduce dose of Imatinib to 400 mg[b].<br>3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d].<br>4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Imatinib until ANC ≥ 1 x10$^9$/L and platelets ≥ 20 x10$^9$/L, then resume treatment at 300 mg[d]. |
| DFSP (starting dose 800 mg) | ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L | 1. Stop Imatinib until ANC ≥ 1.5 x10$^9$/L and platelets ≥ 75 x10$^9$/L.<br>2. Resume treatment with Imatinib at 600 mg<br>3. In the event of recurrence of ANC < 1.0 x10$^9$/L and/or platelets < 50 x10$^9$/L, repeat step 1 and resume Imatinib at reduced dose of 400 mg. |
| ANC = absolute neutrophil count<br>a occurring after at least 1 month of treatment<br>b or 260 mg/m$^2$ in pediatric patients<br>c or 340 mg/m$^2$ in pediatric patients<br>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 (see section PHARMACODYNAMICS AND PHARMACOKINETICS). 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 section WARNINGS AND PRECAUTIONS).

**Hepatic impairment**
Imatinib is mainly metabolized 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 (see sections WARNINGS AND PRECAUTIONS AND SIDE EFFECTS).

**Pediatric patients (below 18 years)**
There is no experience with the use of Imatinib in pediatric 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 pediatric patients in other indications.

Dosing in pediatric patients should be on the basis of body surface area (mg/m$^2$). The dose of 340 mg/m$^2$ daily is recommended for children with chronic phase and advanced phase CML 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. (see sections PHARMACODYNAMICS AND PHARMACOKINETICS).

**Geriatric patients (65 years or above)**
No significant age related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

**Mode of Administration**
Oral route of administration

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

**Warnings and Precautions**
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.

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) (see section INTERACTIONS WITH OTHER MEDICAMENTS).

**Hepatotoxicity**
In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections RECOMMENDED DOSE AND SIDE EFFECTS).

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 (see section SIDE EFFECTS).

**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.

**Tumor lysis syndrome**
Cases of tumor lysis syndrome (TLS) have been reported in patients treated

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with Imatinib. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib (see section SIDE EFFECTS).

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

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 RECOMMENDED DOSE.

**Liver Function**
Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Imatinib. As recommended in section RECOMMENDED DOSE., 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 RECOMMENDED DOSE., 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.

**Pediatric 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 pediatric patients are unknown. Therefore, close monitoring of growth in children under Imatinib treatment is recommended (see section SIDE EFFECTS).

**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, and phenobarbital or hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib. Pretreatment of 14 healthy volunteers with multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of Imatinib, increased Imatinib oral-dose clearance by 3.8 fold (90% confidence interval = 3.5 to 4.3 fold), which represents mean decreases Cmax, AUC (0-24) and AUC(0-∞) by 54%, 68% 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, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. In two published studies, concomitant administration of Imatinib and a product containing St. John's wort led to a 30 to 32% reduction in the AUC of 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. 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.

Drugs that may have their plasma concentration altered by Imatinib

Imatinib increases the mean Cmax 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. cyclosporin or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolized 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 Cmax 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 (Ki 58.5 microM).

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.

**Statement on Usage During Pregnancy and Lactation**
**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 postmarketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. Reproductive studies in rats have demonstrated that imatinib mesylate induced teratogenicity (increased incidence of congenital abnormalities) following prenatal exposure to imatinib mesylate at doses equal to the highest recommended human dose of 800 mg/day based on body surface area. 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 fetus.

**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.

**Infertility**
Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Imatinib during treatment and for at least 15 days after stopping treatment with Imatinib.

**Adverse Effects / Undesirable Effects**
Adverse drug reactions in Table-2 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

**Table 2: 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 failure11*, 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 |

1 Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.
2 Headache was the most common in GIST patients.
3 On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.
4 Flushing was most common in GIST patients and bleeding (hematoma, hemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).
5 Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
6/7 Abdominal pain and gastrointestinal hemorrhage were most commonly observed in GIST patients.
8 Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.
9 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

**Overdose and Treatment**
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.

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

**Adult overdose:**
**1,200 to 1,600 mg** (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite. 1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain. 6,400 mg (single dose): One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

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

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

**Effects on Ability to Drive and Use Machine**
Reports of motor vehicle accidents have been received in patients receiving Imatinib. While most of these reports are not suspected to be caused by Imatinib, 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.

**Instructions for Use**
The prescribed dose should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations.

There is no functional break line in tablet, the score-line on tablet is not intended for breaking the tablet, it is for aesthetic purpose only and for easy to swallowing purpose. Hence the tablet cannot be divided into two equal half doses.

**Storage Conditions**
Store below 30°C.
Protect from moisture.
Store in original package.

**Shelf life**
3 years

**Packaging Available**
Each carton contains 3 x 10's & 6 x 10's PVC/PVdC - Alu blister pack for Imatinib Tablets 100 mg.

Each carton contains 3 x 10's PVC/PVdC - Alu blister pack for Imatinib Tablets 400 mg.

Name and address of the manufacturer:
**Shilpa Medicare Limited,**
Unit-4, Pharmaceutical Formulations SEZ
Plot No's S-20 to S-26, Pharma SEZ, TSIIC,
Green Industrial Park, Polepally (V), Jadcherla (M),
Mahabubnagar (Dt),
509301 Telangana, India.

Name & Address of Product Registration Holder (PRH):
**Unimed Sdn Bhd**
53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara 52200,
Kuala Lumpur, Malaysia.

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