ibakin

Imatinib Mesylate INN Tablet

"Please carefully read the full leaflet"

COMPOSITION

Ibakin 100 mg tablet: Each film coated tablet contains 119.5mg Imatinib Mesylate INN equivalent to 100 mg Imatinib INN.
Ibakin 400 mg tablet: Each film coated tablet contains 478 mg Imatinib Mesylate INN equivalent to 400 mg Imatinib INN.

DESCRIPTION

Imatinib is a small molecule kinase inhibitor. Imatinib Mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino] phenyl] benzamide methane sulfonate. Its molecular formula is C29H31N7O • CH4SO3 and its molecular weight is 589.7.

Imatinib Mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Imatinib Mesylate is soluble in aqueous buffers less than or equal to pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanol, acetone, and acetonitrile.

PHARMACOLOGICAL INFORMATIONS

Mechanism of Action

Imatinib is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients.
In vivo, Imatinib inhibits tumor growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukemia lines derived from CML patients in blast crisis. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, Imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation.

PHARMACOKINETIC PROPERTIES

Absorption and Distribution

Imatinib is well absorbed after oral administration with Cmax achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Mean Imatinib AUC increases proportionally with increasing doses ranging from 25 mg to 1,000 mg. There is no significant change in the pharmacokinetics of Imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady state when Imatinib is dosed once-daily. At clinically relevant concentrations of Imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mostly to albumin and α1-acid glycoprotein.

Elimination

Metabolism

CYP3A4 is the major enzyme responsible for metabolism of Imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows in vitro potency similar to the parent Imatinib. The plasma AUC for this metabolite is about 15% of the AUC for Imatinib. The plasma protein binding of N-demethylated metabolite CGP74588 is similar to that of the parent compound. Human liver microsome studies demonstrated that Imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with Ki values of 27, 7.5, and 8 μM, respectively.

Excretion

Imatinib elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labeled dose of Imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged Imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolite Following oral administration in healthy volunteers, the elimination half-lives of Imatinib and its major active metabolite, the N-dimethyl derivative (CGP74588), are approximately 18 and 40 hours, respectively. Typically, clearance of Imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. The inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment-related toxicity.

THERAPEUTIC INDICATIONS

- **Newly Diagnosed Philadelphia Positive Chronic Myeloid Leuke mia (Ph+ CML)** Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- **Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP)** After Interferon-alpha (IFN) Therapy Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- **Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)** Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- **Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL)** Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
- **Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)** Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test.
- **Aggressive Systemic Mastocytosis (ASM)** Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test)] or with c-Kit mutational status unknown.
- **Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)** Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
- **Dermatofibrosarcoma Protuberans (DFSP)** Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.
- **Kit+ Gastrointestinal Stromal Tumors (GIST)** Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
- **Adjuvant Treatment of GIST** Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

DOSAGE AND ADMINISTRATION

Drug Administration

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. 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).
For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Adult Patients with Ph+ CML CP, AP, or BC

The recommended dose of Imatinib is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult 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 hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6 to 12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

Pediatric Patients with Ph+ CML CP

The recommended dose of Imatinib for children with newly diagnosed Ph+ CML is 340 mg/m2/day (not to exceed 600 mg). Imatinib treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening. There is no experience with Imatinib treatment in children under 1 year of age.

Adult Patients with Ph+ ALL

The recommended dose of Imatinib is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

Pediatric Patients with Ph+ ALL

The recommended dose of Imatinib to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m2/day (not to exceed 600 mg). Imatinib treatment can be given as a once daily dose.

Adult Patients with MDS/MPD

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

Adult Patients with ASM

The recommended dose of Imatinib is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c- Kit mutational status is not known or unavailable, treatment with Imatinib 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. 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.

Adult Patients with HES/CEL

The recommended dose of Imatinib is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. 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.

Adult Patients with DFSP

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

Adult Patients with Metastatic and/or Unresectable GIST

The recommended dose of Imatinib is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increased up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.

Adult Patients with Adjuvant GIST

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 Study 2, three years of Imatinib is recommended. The optimal treatment duration with Imatinib is not known.

DOSE MODIFICATION GUIDELINES

Hepatic impairment

Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Renal Impairment

Patients with moderate renal impairment (CrCL=20–39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL=40–59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment. A dose of 100 mg/day was tolerated in two patients with severe renal impairment.

Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions

If elevations in bilirubin greater than 3 times the institutional upper limit of normal (IULN) or in liver transaminases greater than 5 times the IULN occur, Imatinib should be withheld until bilirubin levels have returned to a less than 1.5 times the IULN and transaminase levels to less than 2.5 times the IULN. In adults, treatment with Imatinib may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m2/day to 260 mg/m2/day. If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Imatinib should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in below.

ASM associated with eosinophilia (starting dose 100 mg)	ANC[1] less than 1.0 x 10^9/L and / or less than 50 x 10^9/L	1. Stop Imatinib until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L 2. Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction)
HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC less than 1.0 x 10^9/L and/or platelets less than 50 x 10^9/L	1. Stop Imatinib until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L 2. Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction)
Ph+ CML: Accelerated Phase and Blast Crisis (starting dose 600 mg) Ph+ ALL (starting dose 600 mg)	ANC less than 0.5 x 10^9/L and/or platelets less than 10 x 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Imatinib to 400 mg 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Imatinib until ANC greater than or equal to1 x 10^9/L and platelets greater than or equal to 20 x 10^9/L and then resume treatment at 300 mg
DFSP (starting dose 800 mg)	ANC less than 1.0 x 10^9/L and/or platelets less than 50 x 10^9/L	1. Stop Imatinib until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L 2. Resume treatment with Imatinib at 600 mg 3. In the event of recurrence of ANC less than 1.0 x 10^9/L and/or platelets less than 50 x 10^9/L, repeat step 1 and resume Imatinib at reduced dose of 400 mg
Pediatric newly diagnosed chronic phase CML (starting dose 340 mg/m2)	ANC less than 1.0 x 10^9/L and/or platelets less than 50 x 10^9/L	1. Stop Imatinib until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L 2. Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction) 3. In the event of recurrence of ANC less than 1.0 x 10^9/L and/or platelets less than 50 x 10^9/L, repeat step 1 and resume Imatinib at reduced dose of 260 mg/m^2

WARNINGS AND PRECAUTIONS

Fluid Retention and Edema

Imatinib is often associated with edema and occasionally serious fluid retention. Weigh and monitor patients regularly for signs and symptoms of fluid retention. Investigate unexpected rapid weight gain carefully and provide appropriate treatment. The probability of edema was increased with higher Imatinib dose and age greater than65 years in the CML studies. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking Imatinib, and in 2%-6% of other adult CML patients taking Imatinib. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking Imatinib, and in 2%-6% of other adult CML patients taking Imatinib. Severe fluid retention was reported in 9% to 13.1% of patients taking Imatinib for GIST.

Hematologic Toxicity

Treatment with Imatinib is associated with anemia, neutropenia, and thrombocytope-

nia.
Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2 to 3 months). In CML, the occurrence of these Cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy.

Congestive Heart Failure and Left Ventricular Dysfunction

Congestive heart failure and left ventricular dysfunction have been reported in patients taking Imatinib. Cardiac adverse reactions were more frequent in patients with advanced age or co-morbidities including previous medical history of cardiac disease.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Imatinib. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Imatinib. Monitor liver function (transaminases, bilirubin, and alkaline phosphatase) before initiation of treatment and monthly, or as clinically indicated. Manage laboratory abnormalities with Imatinib interruption and/or dose reduction. When Imatinib is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended.

Hemorrhage

In a trial of Imatinib versus IFN+Ara-C in patients with the newly diagnosed CML, 1.8% of patients had Grade 3/4 hemorrhage.

Gastrointestinal Disorders

Imatinib is sometimes associated with GI irritation. Imatinib should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

Hypereosinophilic Cardiac Toxicity

In patients with hypereosinophilic syndrome with occult infiltration of HES cells within the myocardium, 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/myeloproliferative disease and systemic mastocytosis may be associated with high eosinophil levels. Consider performing an echocardiogram and determining serum troponin in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, consider prophylactic use of systemic steroids (1–2 mg/kg) for one to two weeks concomitantly with Imatinib at the initiation of therapy.

Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Imatinib. In some cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome reported during post marketing surveillance, a recurrent dermatologic reaction was observed upon re-challenge. Several foreign post marketing reports have described cases in which patients tolerated the reintroduction of Imatinib therapy after resolution or improvement of the bullous reaction. In these instances, Imatinib was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib. Monitor TSH levels in such patients.

Embryo-fetal Toxicity

Imatinib can cause fetal harm when administered to a pregnant woman. Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses approximately equal to the maximum human dose of 800 mg/day based on body surface area. Significant post-implantation loss was seen in female rats administered Imatinib mesylate at doses approximately one-half the maximum human dose of 800 mg/day based on body surface area. Advise sexually active female patients of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) when using Imatinib and for 14 days after stopping Imatinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Growth Retardation in Children and Adolescents

Growth retardation has been reported in children and pre-adolescents receiving Imatinib. The long term effects of prolonged treatment with Imatinib on growth in children are unknown. Therefore, monitor growth in children under Imatinib treatment.

Tumor Lysis Syndrome

Cases of Tumor Lysis Syndrome (TLS), including fatal cases, have been reported in patients with CML, GIST, ALL and eosinophilic leukemia receiving Imatinib. The patients at risk of TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. Monitor these patients closely and take appropriate precautions. Due to possible occurrence of TLS, correct clinically significant dehydration and treat high uric acid levels prior to initiation of Imatinib.

Impairments Related to Driving and Using Machinery

Motor vehicle accidents have been reported in patients receiving Imatinib. Advise patients that they may experience side effects such as dizziness, blurred vision or somnolence during treatment with Imatinib. Recommend caution when driving a car or operating machinery.

ADVERSE REACTIONS

The most frequently reported drug-related adverse reactions were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash.
Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib. The frequency of severe superficial edema was 1.5%–6%.
A variety of adverse reactions represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These reactions appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These reactions were usually managed by interrupting Imatinib treatment and using diuretics or other appropriate supportive care measures. These reactions may be serious or life threatening.

Hematologic and Biochemistry Laboratory Abnormalities

Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses greater than or equal to 750 mg. The occurrence of cytopenias in CML patients was also dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients. The frequency of Grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3- fold higher in blast crisis and accelerated phase compared to chronic phase. The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively. These reactions can usually be managed with either a reduction of the dose or an interruption of treatment with Imatinib, but in rare cases require permanent discontinuation of treatment.

Adverse Reactions in Pediatric Population

Single agent therapy

The overall safety profile of pediatric patients treated with Imatinib in 93 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most commonly reported individual adverse reactions with an incidence similar to that seen in adult patients. Most patients experienced adverse reactions at some time during the study. The incidence of Grade 3/4 events across all types of adverse reactions was 75%; the events with the highest Grade 3/4 incidence in CML pediatric patients were mainly related to myelosuppression.

Adverse Reactions in Other Subpopulations

In older patients (greater than or equal to 65 years old), with the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse reactions. In women, there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen that were related to race but the subsets were too small for proper evaluation.

Acute Lymphoblastic Leukemia

The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps, and rash. Superficial edema was a common finding in all studies and was described primarily as periorbital or lower limb edemas. These edemas were reported as Grade 3/4 events in 6.3% of the patients and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Imatinib.

Myelodysplastic/Myeloproliferative Diseases

Commonly occurred adverse reactions in patients with Myelodysplastic/Myeloproliferative Diseases are nausea, diarrhea, anemia, fatigue, muscle cramp, arthralgia, periorbital edema.

DRUG INTERACTIONS

Agents Inducing CYP3A Metabolism

Concomitant administration of Imatinib and strong CYP3A4 inducers may reduce total exposure of Imatinib; consider alternative agents.

Agents Inhibiting CYP3A Metabolism

Concomitant administration of Imatinib and strong CYP3A4 inhibitors may result in a significant Imatinib exposure increase. Grapefruit juice may also increase plasma concentrations of Imatinib; avoid grapefruit juice.

Interactions with Drugs Metabolized by CYP3A4

Imatinib will increase plasma concentration of CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Use caution when administering Imatinib with CYP3A4 substrates that have a narrow therapeutic window. Because warfarin is metabolized by CYP2C9 and CYP3A4, use low-molecular weight or standard heparin instead of warfarin in patients who require anticoagulation.

Interactions with Drugs Metabolized by CYP2D6

Use caution when administering Imatinib with CYP2D6 substrates that have a narrow therapeutic window.

OVERDOSAGE

Experience with doses greater than 800 mg is limited. Isolated cases of Imatinib overdose have been reported. In the event of over dosage, observe the patient and give appropriate supportive treatment.

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, increase transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.
A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of Imatinib daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse reactions. Another patient developed severe muscle cramps after taking 1,600 mg of Imatinib daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of Imatinib on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse reactions occurred and the patient resumed therapy.

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 experienced decreased white blood cell count and diarrhea.

USE IN SPECIFIC POPULATIONS

Pregnancy

Imatinib can cause fetal harm when administered to a pregnant woman based on human and animal data. There are no clinical studies regarding use of Imatinib in pregnant women. There have been post-market reports of spontaneous abortions and congenital anomalies from women who have been exposed to Imatinib during pregnancy. Reproductive studies in rats have demonstrated that Imatinib Mesylate induced teratogenicity and 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. Advise women to avoid pregnancy when taking Imatinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Lactation

Imatinib and its active metabolite are excreted into human milk. Because of the potential for serious adverse reactions in breastfed infants from Imatinib, advise a lactating woman not to breastfeed during treatment and for 1 month after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Imatinib is harmful to the developing fetus. Test pregnancy status in females with reproductive potential prior to the initiation of treatment with Imatinib.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Imatinib during treatment and for fourteen days after stopping treatment with Imatinib.

Infertility

The risk of infertility in females or males of reproductive potential has not been studied in humans. In a rat study, the fertility in males and females was not affected.

Pediatric Use

The safety and effectiveness of Imatinib have been demonstrated in pediatric patients with newly diagnosed Ph+ chronic phase CML and Ph+ ALL. There are no data in children under 1 year of age.

Geriatric Use

In the CML clinical studies, approximately 20% of patients were older than 65 years. In the study of patients with newly diagnosed CML, 6% of patients were older than 65 years. The frequency of edema was higher in patients older than 65 years as compared to younger patients; no other difference in the safety profile was observed.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of both Imatinib and its major metabolite, CGP74588, was assessed in 84 patients with cancer with varying degrees of hepatic impairment at Imatinib doses ranging from 100 mg to 800 mg. Mild and moderate hepatic impairment do not influence exposure to Imatinib and CGP74588. In patients with severe hepatic impairment, the Imatinib Cmax and area under curve (AUC) increased by 63% and 45% and the CGP74588 Cmax and AUC increased by 56% and 55%, relative to patients with normal hepatic function.

Renal Impairment

There are not sufficient data in patients with severe renal impairment. Dose reductions are necessary for patients with moderate and severe renal impairment.

PHARMACEUTICAL INFORMATIONS

Storage and Condition

Store below 30°C. Protect from moisture. Dispense in a tight container. Imatinib is a cytotoxic drug. Follow applicable special handling and disposal procedures. Do not crush Imatinib tablets. Avoid direct contact of crushed tablets with the skin or mucous membranes. If such contact occurs, wash thoroughly. Avoid exposure to crushed tablets.
Keep out of the reach of children.
To be dispensed only on the prescription of a registered physician.

PRESENTATION AND PACKAGING

Ibakin-100 tablets: Each commercial box contains 1x10's tablets in Alu-Alu blister pack.
Ibakin-100 tablets: Each commercial box contains 2x10's tablets in Alu-Alu blister pack.
Ibakin-100 tablets: Each commercial box contains 3x10's tablets in Alu-Alu blister pack.
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Ibakin-400 tablets: Each commercial box contains 6x10's tablets in Alu-Alu blister pack.

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