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OVERDOSAGE
Experience with doses greater than 800 mg is limited. In the event of over dosage, the patient should be observed and appropriate supportive treatment given. An oral dose of 1200 mg/m2/day, approximately 2.5 times the human dose of 800 mg, based on body surface area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m2 /day, approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10 administrations, due to general deterioration of the animals with secondary many tissues.

PRESENTATION
Imanib 100mg Tablet available in blister pack of 6x10's
Imanib 400mg Tablet available in blister pack of 3x10's

INSTRUCTIONS:
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات :
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔ (درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے) ۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

ART No. 1603

Imanib

(Imatinib Mesylate)

ایمانِب

(ایماٹینب میسائیلیٹ)

100mg & 400mg Tablets

۱۰۰ ملی گرام اور ۴۰۰ ملی گرام گولیاں

COMPOSITION:
Imanib Tablet 100mg
Each film coated tablet contains:
Imatinib Mesylate Eq. to Imatinib.....100mg

Imanib Tablet 400mg
Each film coated tablet contains:
Imatinib Mesylate Eq. to Imatinib.....400mg

CLINICAL PHARMACOLOGY
DESCRIPTION
Imatinib is a small molecule kinase inhibitor used to treat certain types of cancer. It is used in treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies.

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

PHARMACOKINETICS
The pharmacokinetics of IMANIB have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 500 patients. Imatinib is well absorbed after oral administration with Cmax achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule formulation is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25-1000 mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when IMANIB 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 a1-acid glycoprotein.

Metabolism and elimination
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. Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14 61 C-labelled 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 metabolites. 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. However, 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.

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SPECIAL POPULATION
Pediatric: There are no pharmacokinetic data in pediatric patients.
Hepatic Insufficiency: No clinical studies were conducted with IMANIB in patients with impaired hepatic function.
Renal Insufficiency: No clinical studies were conducted with IMANIB in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

THERAPEUTIC INDICATIONS
Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (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.

Hyper eosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)
Adult patients with hyper eosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRa fusion kinase (mutational analysis or FISH demonstration of CH1C2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRa 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 & ADMINISTRATION
Adult Patients with Ph+ CML CP, AP, or BC
The recommended dose of Imanib 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 Imanib for children with newly diagnosed Ph+ CML is 340 mg/m2/day (not to exceed 600 mg). Imanib 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 Imanib treatment in children under 1 year of age.

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

Pediatric Patients with Ph+ ALL
The recommended dose of Imanib to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m7day (not to exceed 600 mg). Imanib treatment can be given as a once daily dose.

Adult Patients with MDS/MPD
Determine PDGFRb gene rearrangements status prior to initiating treatment. The recommended dose of Imanib is 400 mg/day for adult patients with MDS/MPD.

Adult Patients with ASM
Determine D816V c-Kit mutation status prior to initiating treatment. The recommended dose of Imanib 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 Imanib 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-PDGFRa, 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 Imanib is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRa 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 Imanib is 800 mg/day for adult patients with DFSP. Adult Patients with Metastatic and/or Unresectable GIST The recommended dose of Imanib is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase 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.

METHOD OF ADMINISTRATION
For oral administration only.

ADVERSE REACTIONS
Complications of advanced CML and co-administered medications make causality of adverse events difficult to assess in single arm studies. The majority of IMANIB-treated patients experienced adverse events at some time. Most events were of mild to moderate grade, but drug was discontinued for adverse events in 1% of patients in chronic phase, 2% in accelerated phase and 5% in blast crisis. The most frequently reported drug-related adverse events were nausea, vomiting, edema, and muscle cramps. Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of IMANIB. The frequency of severe edema was 1-5%. A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events 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 events were usually managed by interrupting IMANIB treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

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Hematologic toxicity:
Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses > 750 mg (phase I study). The occurrence of cytopenias was also dependent on the stage of the disease, with a frequency of grade 3 or 4 neutropenia and thrombocytopenia 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 ranged usually from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with IMANIB, but in rare cases require permanent discontinuation of treatment.

Hepatotoxicity:
Severe elevation of transaminases or bilirubin occurred in 1.1-3.5% and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

Adverse Effects in Subpopulations:
With the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse events in older patients (>65 years old). With the exception of a slight increase in the frequency of grade 1/2 periorbital edema, headache and fatigue in women, there was no evidence of a difference in the incidence or severity of adverse events between the sexes. No differences were seen related to race but the subsets were too small for proper evaluation.

CONTRAINDICATIONS
Use of IMANIB is contraindicated in patients with hypersensitivity to imatinib or to any other component of IMANIB.

PRECAUTIONS
Pregnancy
Pregnancy Category D
Women of childbearing potential should be advised to avoid becoming pregnant. Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses > 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered this dose also experienced significant post-implantation loss in the form of early fetal resorption. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. These effects were not seen at doses <30 mg/kg (one-third the maximum human dose of 161 800 mg). There are no adequate and well-controlled studies in pregnant women. If IMANIB is used during pregnancy, or if the patient becomes pregnant while taking (receiving) IMANIB, the patient should be apprised of the potential hazard to the fetus.

Pediatric Use
The safety and effectiveness of IMATINIB in pediatric patients have not been established.

Geriatric Use
In the clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of IMANIB was similar in older and younger patients.

General
Fluid retention and edema: IMANIB is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher imatinib dose and age > 65 years. Severe fluid retention (pleural effusion, pericardial effusion, pulmonary edema, and ascites) was reported in 1 to 2% of patients taking IMANIB. In addition, severe superficial edema was reported in 1-3% of the patients.

GI irritation: IMANIB is sometimes associated with GI irritation. IMANIB should be taken with food and a large glass of water to minimize this problem.

Hematologic toxicity: Treatment with IMANIB is often associated with neutropenia or thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). 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.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with IMANIB. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with IMANIB. Patients with hepatic impairment should be closely monitored because exposure to IMANIB may be increased. As there are no clinical studies of IMANIB in patients with impaired liver function, no specific advice concerning initial dosing adjustment can be given.

Toxicities from long-term use: Because follow-up of most patients treated with imatinib is relatively short (< 6 mos), there are no long-term safety data on IMANIB treatment. It is important to consider potential toxicities suggested by animal studies, specifically, liver and kidney toxicity and immunosupression. Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunitic infections was observed occur with chronic imatinib treatment. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with imatinib mesylate. Positive genotoxic effects were obtained for imatinib in an in vitro mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an in vitro bacterial cell assay (Ames test), an in vitro mammalian cell assay (mouse lymphoma) and an in vivo rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses < 20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females. At a dose of 60 mg/kg (approximately equal to the human dose of 800 mg) female rats had significant post implantation fetal loss and a reduced number of live fetuses. This was not seen at doses < 20 mg/kg (one-fourth the maximum human dose of 800mg).

DRUG INTERACTIONS
Drugs that may increase imatinib plasma concentrations: Caution is recommended when administering IMANIB with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when IMANIB is co-administered with ketoconazole (CYP3A4 inhibitor).

Drugs that may decrease imatinib plasma concentrations: Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Comedications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may reduce exposure to IMANIB. No specific studies have been performed and caution is recommended.

Drugs that may have their plasma concentration altered by IMANIB
Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib. Particular caution is recommended when administering IMANIB with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). IMANIB will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.) Because warfarin is metabolized by CYP2C9, patients who require anticoagulation should receive 226 low-molecular weight or standard heparin. In vitro, IMANIB inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when co-administered with IMANIB. No specific studies have been performed and caution is recommended.