IMAXEN

Imatinib 100 mg & 400 mg tablets

Everest

COMPOSITION

IMAXEN 100 tablet: Each film coated tablet contains Imatinib Mesilate BP equivalent to Imatinib 100 mg.

IMAXEN 400 tablet: Each film coated tablet contains Imatinib Mesilate BP equivalent to Imatinib 400 mg.

PHARMACOLOGY

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:

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 1-acid glycoprotein.

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.

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 metabolites. Following oral administration in healthy volunteers, the elimination half-lives of Imatinib and its major active metabolite, the N-demethyl derivative (CGP74588), are approximately 18 and 40 hours, respectively.

INDICATION

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in chronic phase.
- 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 relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy
- Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDG-FRα fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
- Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

DOSAGE AND ADMINISTRATION

- Adults with Ph+ CML CP : 400 mg/day
- Adults with Ph+ CML AP or BC: 600 mg/day
- Pediatrics with Ph+ CML CP: 340 mg/m^2/day
- Adults with Ph+ ALL: 600 mg/day
- Pediatrics with Ph+ ALL: 340 mg/m^2/day
- Adults with MDS/MPD: 400 mg/day
- Adults with ASM: 100 mg/day or 400 mg/day
- Adults with HES/CEL: 100 mg/day or 400 mg/day
- Adults with DFSP: 800 mg/day
- Adults with metastatic and/or unresectable GIST: 400 mg/day
- Adjuvant treatment of adults with GIST: 400 mg/day
- Patients with mild to moderate hepatic impairment: 400 mg/day
- Patients with severe hepatic impairment: 300 mg/day

All doses of Imatinib should be taken 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. Imatinib can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400-mg tablet to reduce exposure to iron.

CONTRAINDICATION

None.

WARNING & PRECAUTION

- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics.
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction, dose interruption, or discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter.
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Monitor and treat patients with cardiac disease or risk factors for cardiac failure.
- Severe hepatotoxicity, including fatalities may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction.
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST.
- Gastrointestinal (GI) perforations, some fatal, have been reported.
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Imatinib in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD, and ASM).
- Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Imatinib.
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients.
- Fetal harm can occur when administered to a pregnant woman. Apprise women of the potential harm to the fetus, and to avoid pregnancy when taking Imatinib.
- Growth retardation occurring in children and pre-adolescents receiving Imatinib has been reported. Close monitoring of growth in children under Imatinib treatment is recommended.
- Tumor Lysis Syndrome. Close monitoring is recommended.
- Reports of motor vehicle accidents have been received in patients receiving Imatinib. Caution patients about driving a car or operating machinery.
- Renal Toxicity. A decline in renal function may occur in patients receiving Imatinib. Evaluate renal function at baseline and during therapy, with attention to risk factors for renal dysfunction.

SIDE EFFECTS

The following serious adverse reactions are described elsewhere in the labeling:

- Fluid Retention and Edema
- Hematologic Toxicity
- Congestive Heart Failure and Left Ventricular Dysfunction
- Hepatotoxicity
- Hemorrhage
- Gastrointestinal Disorders
- Hypereosinophilic Cardiac Toxicity
- Dermatologic Toxicities
- Hypothyroidism
- Growth Retardation in Children and Adolescents
- Tumor Lysis Syndrome
- Impairments Related to Driving and Using Machinery
- Renal Toxicity

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.

USE IN SPECIFIC POPULATION

Fertility, Pregnancy and Lactation.

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during treatment and for at least 15 days after stopping treatment with Imatinib.

Pregnancy

There are limited data on the use of imatinib in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. Studies in animals have however shown reproductive toxicity and the potential risk for the foetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

There is limited information on imatinib distribution on human milk. Studies in two breast-feeding women revealed that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women should not breast-feed during treatment and for at least 15 days after stopping treatment with Imatinib.

Fertility

In non-clinical studies, the fertility of male and female rats was not affected, although effects on reproductive parameters were observed. Studies on patients receiving Imatinib and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on Imatinib treatment should consult with their physician.

OVERDOSE

Experience with doses higher than the recommended therapeutic dose is limited. In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was “improved” or “recovered”. Events that have been reported at different dose ranges are as follows:

Adult Population

1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.

6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.

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

Paediatric population

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

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

PHARMACEUTICAL INFORMATION

Storage Condition

Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED

IMAXEN 100 tablet: Each HDPE container contains 30 film coated tablets each of which contains Imatinib Mesilate BP equivalent to Imatinib 100 mg.

IMAXEN 400 tablet: Each HDPE container contains 14 film coated tablets each of which contains Imatinib Mesilate BP equivalent to Imatinib 400 mg.

Manufactured by

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