For use of a Registered Medical Oncologist or a Hospital or a Laboratory

Imatinib Capsules 100 mg

Imatib®

Composition

Each capsule contains
Imatinib ..... 100 mg
(as mesylate)
Approved colours used
in empty capsule.

13032400

Description

Imatib capsules contain imatinib mesylate equivalent to 100 mg of imatinib freebase. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1- piperazinyl) methyl]-N-[4- methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]aminolphenyl] benzamide methanesulfonate.

Imatinib mesylate 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 chronic myeloid leukemia (CML).

Imatib 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 gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

Indication and Usage

Imatib is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy.

Imatib is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant GIST.

Dosage and Administration

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

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. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Recommended dosage of Imatinib mesylate for patients in:

- Chronic phase CML is - 400 mg/day
- Accelerated phase or blast crisis is - 600 mg/day
- Unresectable and/or metastatic, malignant GIST- 400 mg/day or 600 mg/day

In CML, dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 to 800 mg (given as 400 mg twice 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 hematologic response after at least 3 months of treatment; loss of a previously achieved hematologic response.

Dose adjustment for Hepatotoxicity and Other Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Imatinib mesylate should 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 mesylate 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 mesylate may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to 400 mg).

Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended.

Pediatric

The safety and efficacy of Imatinib mesylate in patients under the age of 18 years have not been established.

Contraindications

Use of Imatinib mesylate is contraindicated in patients with hypersensitivity to imatinib or to any other component of imatinib mesylate.

Warnings

Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant. If imatinib mesylate is used during pregnancy or if the patient becomes pregnant while taking imatinib mesylate the patient should be apprised of the potential hazard to the fetus.

Precautions

- Fluid retention and Edema: Imatinib mesylate 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.
- GI irritation: Imatinib mesylate is sometimes associated with GI irritation. Imatinib mesylate should be taken with food and a large glass of water to minimize this problem.
- Hemorrhage: In patients with GIST, gastrointestinal bleeds or intra-tumoral bleeds or both may occur from gastrointestinal tumor sites.
- Hematologic Toxicity: Treatment with Imatinib mesylate is 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. In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with chronic phase CML (See Dosage and Administration).
- Hepatoxicity: Hepatotoxicity, occasionally severe, may occur with Imatinib mesylate. 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 Imatinib mesylate. (See Dosage and Administration). Patients with hepatic impairment should be closely monitored because exposure to Imatinib mesylate may be increased. As there are no clinical studies of Imatinib mesylate 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, there are no long term safety data.

Drug Interactions

- Drugs that may increase imatinib plasma concentrations: Caution is recommended when administering imatinib mesylate 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 Imatinib mesylate is coadministered 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. Co-medications that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, Phenobarbital or St. John's Wort) may reduce exposure to Imatinib mesylate.
- Drugs that may have their plasma concentration altered by Imatinib mesylate:

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 Imatinib mesylate with CYP3A4 substrates that have a narrow therapeutic window (e.g. cyclosporine or pimozide). Imatinib mesylate will increase plasma concentrations 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 and CYP3A4, patients who require anticoagulation should receive low molecular weight or standard heparin.

In vitro, Imatinib mesylate inhibits the cytochrome P450 isoenzymes CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when co-administered with Imatinib mesylate. No specific studies have been performed and caution is recommended.

- Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate. 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 vitro rat micronucleus assay. In male rats maximum clinical dose caused decrease in testicular and epididymal weights and percent motile sperms. At maximum clinical dose, female rats had significant post implantation fetal loss and a reduced number of live fetuses. These effects on fertility were not seen with use of lower doses.

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk.

Pediatric Use

The safety and effectiveness of Imatinib mesylate in pediatric patients have not been established.

Geriatric Use

The efficacy of Imatinib mesylate was similar in older and younger patients.

Adverse Reactions

- Chronic Myeloid Leukemia

Majority of Imatinib mesylate treated patients experience adverse events at some time. Most events are mild to moderate grade. The most frequently reported drug-related adverse events are nausea, vomiting, diarrhea, edema, and muscle cramps. Edema is most frequently periorbital or in lower limbs and is managed with diuretics, other supportive measures, or by reducing the dose of Imatinib mesylate. (See Dosage and Administration).

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, are more common in the blast crisis and accelerated phase studies (where the dose is 600 mg/day), and are common in the elderly. These events are usually managed by interrupting Imatinib mesylate treatment and with diuretics or other appropriate supportive care measures.

- Hematologic Toxicity

Cytopenias, and particularly neutropenia and thrombocytopenia, are seen in CML. The occurrence of cytopenias in CML patients is 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.

- Hepatotoxicity

Elevation of transaminases or bilirubin may occur. It is usually managed with dose reduction or interruption.

- Gastrointestinal Stromal Tumors

Majority of Imatinib mesylate patients experience adverse events at some time. The most frequently reported adverse events are edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue and rash. Most events are of mild to moderate severity.

Overdosage

Experience with doses greater than 800mg is limited. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

Storage

Do not store above 30°C.

Presentation

Imatib: Blister of 10 capsules

IMBC-0000-LF-00

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Cipla

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Sobhan Oncology	
Leaflet	Imatib®
Color	Black
Size	120x320 (*Tolerance: ±1mm*)
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