Imatinib mesylate

Category:

Protein-Tyrosine kinase inhibitor / Antineoplastic Agent

Pharmacokinetics:

Imatinib mesylate is well absorbed after oral doses with peak blood concentrations occurring after 2 to 4 hours. The mean bioavailability is about 98%. Imatinib is reported to be about 95% bound to plasma proteins. Plasma elimination half-lives of imatinib and its major active metabolite, the *N*-demethylated piperazine derivative, are about 18 and 40 hours respectively. The major enzyme responsible for the metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4; isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role. About 81% of a dose is eliminated within 7 days in the faeces (68%) and urine (13%). It is excreted mostly as metabolites, with only 25% as unchanged drug.

Mechanism of action:

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 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.

Indications:

- Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

- Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy
- Pediatric Patients with Ph+ CML in Chronic Phase
- Ph+ Acute Lymphoblastic Leukemia (ALL)
- Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)
- Aggressive Systemic Mastocytosis (ASM)
- Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)
- Dermatofibrosarcoma Protuberans (DFSP)
- Kit+ Gastrointestinal Stromal Tumors (GIST)
- Adjuvant Treatment of GIST

Administration and Dosage:

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.

In children, imatinib treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with imatinib treatment in children under 2 years of age.

Adult Patients with Ph+ CML CP, AP and 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 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 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

Pediatric Patients with Ph+ CML

The recommended dose of imatinib for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). The recommended imatinib dose is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

Ph+ ALL

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

MDS/MPD

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

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.

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.

DFSP

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

GIST

The recommended dose of imatinib 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.

The recommended dose of imatinib is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In the clinical study, imatinib was administered for one year.

Contraindications:

Imatinib is contraindicated in patients with known hypersensitivity to imatinib or to any of its components.

Precautions:

- Fluid Retention and Edema: 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.
- Hematologic Toxicity (anemia, neutropenia, and thrombocytopenia)
- Severe Congestive Heart Failure and Left Ventricular Dysfunction
- Hepatotoxicity: Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly, or as clinically indicated.
- Hemorrhage
- Gastrointestinal Disorders: imatinib should be taken with food and a large glass of water to minimize this problem.
- Hypereosinophilic Cardiac Toxicity
- Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of imatinib.
- Hypothyroidism: TSH levels should be closely monitored in such patients.

Pregnancy and breast feeding:

Pregnancy: Category D

Lactation: Because of the potential for serious adverse reactions in nursing infants from imatinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Side effects:

- fever, sore throat, and headache with a severe blistering, peeling, and red skin rash
- nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes)
- fever, chills, body aches, flu symptoms
- black, bloody, or tarry stools
- coughing up blood or vomit that looks like coffee grounds
- pale skin, easy bruising or bleeding, unusual weakness
- feeling short of breath, even with mild exertion
- swelling, rapid weight gain
- urinating more or less than usual, or not at all
- sudden, severe headache or pain behind the eyes

Drug Interactions:

- Agents Inducing CYP3A Metabolism: decrease imatinib concentrations (e.g.: rifampin)
- Agents Inhibiting CYP3A Metabolism: Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole and Grapefruit juice).
- Interactions with Drugs Metabolized by CYP3A4: Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate). Particular caution is recommended when administering imatinib with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus or tacrolimus).
  Imatinib 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 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin instead of warfarin.
- Interactions with Drugs Metabolized by CYP2D6: Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with imatinib.
- Interaction with Acetaminophen: Systemic exposure to acetaminophen is expected to be increased when co-administered with imatinib.

Packaging:

Imatinib is available as 100 mg F.C tablets in box of 30 tablets.

Storage:

- Store below 30 °C
- Protect from moisture and light
- Keep out of the reach of children