Tyronib®

Imatinib INN

Presentation

Tyronib®100 mg tablet: Each film-coated tablet contains Imatinib mesylate INN 119.47 mg equivalent to Imatinib 100 mg.
Tyronib® 400 mg tablet: Each film-coated tablet contains Imatinib mesylate INN 477.88 mg equivalent to Imatinib 400 mg.

Description

Imatinib mesylate is a small molecule protein Tyrosine Kinase Inhibitor. It inhibits the activity of several tyrosine kinases: c-KIT, the receptor for stem cell factor coded by the c-Kit proto-oncogene, the Platelet-Derived Growth Factor Receptors (PDGFR), the Abl family of non-receptor tyrosine kinases consisting of Abl and Arg (the Abl-related gene), and c-Fms, the receptor for macrophage-stimulating factor. Malignancies mediated through these pathways are the primary target for Imatinib.

Therapeutic indication

Imatinib is a kinase inhibitor indicated for the treatment of:

- 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 (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) 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 (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- Adjuvant treatment of adult patients following 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

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. 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 in CML and Ph+ ALL. Alternatively, in children with CML 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.
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.

Dose Modification Guidelines

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Imatinib should be increased by at least 50%, and clinical response should be carefully monitored.
Hepatic Impairment: Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated as 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.

Drug Interactions

Agents Inhibiting CYP3A4 Metabolism
There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Imatinib was coadministered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering Imatinib with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.
Interactions with Drugs Metabolized by CYP3A4
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 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
Imatinib increased the mean Cmax and AUC of metoprolol by approximately 23% suggesting that Imatinib has a weak inhibitory effect on CYP2D6-mediated metabolism. No dose adjustment is necessary, however, caution is recommended when administering Imatinib with CYP2D6 substrates that have a narrow therapeutic window.
Interaction with Acetaminophen
In vitro, Imatinib inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 _M). Coadministration of Imatinib (400 mg/day for eight days) with acetaminophen (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen. Imatinib pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of Imatinib at doses >400 mg/day or the chronic use of concomitant acetaminophen and Imatinib.

Contraindications

None.

Side effects

Very common:
Weight gain (signs of water retention), headache, nausea, vomiting, diarrhea, indigestion, abdominal pain, itchy red burning rash, muscle cramps, muscle, bone, and joint pain, fatigue (tiredness).
Common:
Loss of appetite, dizziness, taste disturbance, tingling, pain or numbness of the hands, feet, legs or around the hip, difficulty sleeping, discharge from the eye with itching, redness and swelling (conjunctivitis), blurred vision, increased tear production, dry eye, nose bleeds, swelling in the abdomen, gas (flatulence), constipation, heartburn, nausea and stomach pain (sign of gastritis), dry mouth, itching, dry skin, unusual hair loss or thinning, night sweats, weakness, increased muscle tension, hypersensitivity (allergies), decreased skin sensitivity, increased sensitivity of the skin to sun (sign of photosensitivity), hot flushes, chills, decreased weight, mouth ulceration, joint swelling, abnormal liver test results, cough, fever, and swelling of the eyelids or around the eye.

Precautions

- Severe heart failure and decrease in the amount of blood pumped by the heart
- Rhabdomyolysis has been rarely observed
- Serious bleeding
- Water retention
- Liver failure (in some cases, fatal)
- Gastrointestinal perforation (a hole through the wall of the stomach or small intestine, or large bowel) in some cases, fatal.

Pregnant Women

Sexually active female patients should use highly effective contraception during treatment. Imatinib can cause fetal harm when administered to a pregnant woman. There have been postmarket reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. Imatinib was teratogenic in animals. Women should be advised not to become pregnant when taking Imatinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers

Imatinib and its active metabolite are excreted into human milk. Based on data from three breastfeeding women taking Imatinib, the milk: plasma ratio is about 0.5 for imatinib and about 0.9 for the active metabolite. Considering the combined concentration of imatinib and active metabolite, a breastfed infant could receive up to 10% of the maternal therapeutic dose based on body weight. 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.

Pediatric Use

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

Overdosage

Adult overdose:
1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite, increased bilirubin and liver transaminase level.
1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased bilirubin, gastrointestinal pain.
6,400 mg (single dose): A case report in the literature about one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Pediatric overdose:
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 dose experienced decreased white blood cell count and diarrhea.

Storage

Store at temperature not exceeding 30°C in a dry place. Protect from light and moisture.

Packaging

Tyronib® 100 mg tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.
Tyronib® 400 mg tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Medicine : Keep out of reach of children

For further information, please contact: 01977 158 926
(9.00 am - 5.00 pm)

Healthcare

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