Metanib

Imatinib INN 400 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Imatinib 400 mg as Imatinib Mesylate INN.

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.

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 Metanib 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 α1-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.

Indications:

Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML): Metanib is indicated for the treatment of 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: Metanib is indicated for the treatment of 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): Metanib is indicated for the treatment of adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

Pediatric Patients with Ph+ Acute Lymphoblastic Leukemia (ALL): Metanib is indicated for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD): Metanib is indicated for the treatment of 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): Metanib is indicated for the treatment of adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test.

Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL): Metanib is indicated for the treatment of adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.

Dermatofibrosarcoma Protuberans (DFSP): Metanib is indicated for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.

Kit+ Gastrointestinal Stromal Tumors (GIST): Metanib is indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

Adjuvant Treatment of GIST: Metanib is indicated for the adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

Dosage and Administration:

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. 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.

Adult Patients with Ph+ CML CP, AP, or BC: The recommended dose of Metanib 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 Metanib for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). Metanib 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 Metanib treatment in children under 1 year of age.

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

Pediatric Patients with Ph+ ALL: The recommended dose of Metanib to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m²/day (not to exceed 600 mg). Metanib treatment can be given as a once daily dose.

Adult Patients with MDS/MPD: The recommended dose of Metanib is 400 mg/day for adult patients with MDS/MPD.

Adult Patients with ASM: The recommended dose of Metanib is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. 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.

Adult Patients with HES/CEL: The recommended dose of Metanib 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.

Adult Patients with DFSP: The recommended dose of Metanib is 800 mg/day for adult patients with DFSP.

Adult Patients with Metastatic and/or Unresectable GIST: The recommended dose of Metanib 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, 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 Metanib is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. Or, as directed by the registered physicians.

Dose Modification:

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 Gleevec 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 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.

Side Effects:

- 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

Contraindication: It is contraindicated in patients with hypersensitivity to Imatinib or any other components of this product.

Use in Pregnancy and Lactation: Pregnancy category D. It can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid pregnancy when taking Metanib. 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.

Lactation: Imatinib and its active metabolite are excreted into human milk. Because of the potential for serious adverse reactions in breastfed infants from Metanib, a lactating woman should be advised not to breastfeed during treatment and for 1 month after the last dose.

Contraception: Females: Female patients of reproductive potential should be advised to use effective contraception when using Metanib during treatment and for fourteen days after stopping treatment with Metanib.

Pediatric Use: The safety and effectiveness of Metanib have been demonstrated in pediatric patients with newly diagnosed Ph+ chronic phase CML and Ph+ ALL.

Drug Interactions:

Agents Inducing CYP3A Metabolism: Concomitant administration of Metanib and strong CYP3A4 inducers may reduce total exposure of Imatinib; alternative agents should be considered.

Agents Inhibiting CYP3A Metabolism: Concomitant administration of Metanib and strong CYP3A4 inhibitors may result in a significant Imatinib exposure increase. Grapefruit juice may also increase plasma concentrations of Imatinib; so it should be avoided.

Interactions with Drugs Metabolized by CYP3A4: Metanib will increase plasma concentration of CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Caution should be used when administering Metanib with CYP3A4 substrates that have a narrow therapeutic window. Because warfarin is metabolized by CYP2C9 and CYP3A4, low-molecular weight or standard heparin should be used instead of warfarin in patients who require anticoagulation.

Interactions with Drugs Metabolized by CYP2D6: Caution should be used when administering Metanib with CYP2D6 substrates that have a narrow therapeutic window.

Precautions:

Fluid Retention and Edema: Metanib is often associated with edema and occasionally serious fluid retention. Weigh and monitor patients regularly for signs and symptoms of fluid retention. Investigate unexpected rapid weight gain carefully and provide appropriate treatment. The probability of edema was increased with higher Metanib dose and age greater than 65 years in the CML studies. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking Metanib, and in 2%-6% of other adult CML patients taking Metanib. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking Metanib, and in 2%-6% of other adult CML patients taking Metanib. Severe fluid retention was reported in 9% to 13.1% of patients taking Gleevec for GIST. In a randomized trial in patients with newly diagnosed Ph+CML in chronic phase comparing Metanib and Nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Metanib and in 3.9% of patients receiving Nilotinib 300 mg twice daily. Effusions (including pleural effusion, pericardial effusion, ascites) or pulmonary edema were observed in 2.1% (none were Grade 3 or 4) of patients in the Metanib arm and 2.2% (0.7% Grade 3 or 4) of patients in the Nilotinib 300 mg twice daily arm.

Hematologic Toxicity: Treatment with Metanib is associated with anemia, neutropenia, and thrombocytopenia. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2 to 3 months). In CML, 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. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy.

Congestive Heart Failure and Left Ventricular Dysfunction: Congestive heart failure and left ventricular dysfunction have been reported in patients taking Metanib. Cardiac adverse reactions were more frequent in patients with advanced age or co-morbidities including previous medical history of cardiac disease.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Metanib. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Metanib. Monitor liver function (transaminases, bilirubin, and alkaline phosphatase) before initiation of treatment and monthly, or as clinically indicated.

Hemorrhage: In a trial of Metanib versus IFN+Ara-C in patients with the newly diagnosed CML, 1.8% of patients had Grade 3/4 hemorrhage. In the Phase 3 unresectable or metastatic GIST studies, 211 patients (12.9%) reported Grade 3/4 hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 7 patients (5%) had a total of 8 CTC Grade 3/4 hemorrhages; gastrointestinal (GI) (3 patients), intra-tumoral (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI hemorrhages.

Gastrointestinal Disorders: Metanib is sometimes associated with GI irritation. Metanib should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

Hypereosinophilic Cardiac Toxicity: In patients with hypereosinophilic syndrome with occult infiltration of HES cells within the myocardium, cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Metanib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Metanib.

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Metanib. In some cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome reported during postmarketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge.

Hypothyroidism: Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Metanib. Monitor TSH levels in such patients.

Growth Retardation in Children and Adolescents: Growth retardation has been reported in children and pre-adolescents receiving Metanib.

Tumor Lysis Syndrome: Cases of Tumor Lysis Syndrome (TLS), including fatal cases, have been reported in patients with CML, GIST, ALL and eosinophilic leukemia receiving Metanib. The patients at risk of TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment.

Overdose:

Adult Overdose: 1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite. **1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days):** Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain. 6,400 mg **(single dose):** One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increase 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, diarrhea and anorexia and another 3-year-old male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhea.

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

Packaging: Each box contains 28 tablets in a blister pack.