Imatinib capsule

IMATINIB

Composition
Each capsule contains: Imatinib (as mesylate) 100 mg

Description
Imatinib capsule 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)-2pyriminyl] Aminolphenyl] benzamide methanesulfonate.
Imatinib mesylate, a specific inhibitor of Bcr-Abl tyrosine kinase, is an antineoplastic agent that is structurally and pharmacologically distinct from other currently available antineoplastic agents.
The Philadelphia chromosome, characteristic of chronic myelogenous leukemia (CML), is created by a reciprocal translocation. Translocation between chromosomes results in production of an abnormal protein (Bcr-Abl tyrosine kinase) that exhibits enhanced tyrosine kinase activity.
Imatinib competitively inhibits Bcr-Abl tyrosine kinase, The drug has been shown to inhibit proliferation and induce apoptosis of Bcr-Abl positive cells as well as fresh leukemic cells from Philadelphia chromosome positive CML. Imatinib also appears to inhibit receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and PDGF mediated and SCF-media cellular events. Data from in vitro studies shows that imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells.

Pharmacokinetic
Absorption
Bioavailability: 98%
Peak Plasma Time: 2-4 hr.
Distribution
Protein Binding: 95%
Metabolism
Metabolized mostly by CYP3A4
Enzymes inhibited: CYP2D6, CYP3A4
Elimination
Half-Life: 18 hr. (parent drug); 40 hr. (metabolite)
Clearance: 8-14 L/hr.
Excretion:
Approximately 81% of the dose was eliminated within 7 days in feces (68%), urine(13%)
Dialyzable: no

Dosage and Administration
Adult

1. Acute Lymphoblastic Leukemia
   for adults with relapsed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) 600 mg PO qDay
2. Myelodysplastic/Myeloproliferative Diseases
   Indicated in adults with myelodysplastic/ myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements 400 mg PO qDay
3. Hypereosinophilic Syndrome/Eosinophilic Leukemia
   Indicated for adults with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR-alpha fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR-alpha fusion kinase negative or unknown 400 mg PO qDay
   *In patients with demonstrated F1P1L1-PDGFR-alpha fusion kinase: 100 mg PO qDay; may increase to 400 mg qDay in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy
4. Chronic Myeloid Leukemia
   Chronic phase
   • Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase
   • 400 mg PO qDay
   Accelerated phase or blast crisis
   • 600 mg PO qDay
   • May increase to 400 mg PO q12hr
5. Dermatofibrosarcoma Protuberances
   Indicated for adults with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans 400 mg PO q12hr
6. Aggressive Systemic Mastocytosis
   Indicated for adults with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown Without D816V c-Kit mutation: 100 mg PO qDay, c-Kit mutational status unknown: 400 mg PO qDay if not responding to other therapies.
7. Gastrointestinal Stromal Tumors
   Unresectable and/or metastatic malignant GIST
   • 400 mg PO qDay; may increase to 400 mg BID in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions
   Adjuvant treatment following complete gross resection of GIST
   • 400 mg PO qDay x 3 years

Pediatric

1. Chronic Myeloid Leukemia
Indicated for newly diagnosed adult and pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase
<1 year: Safety and efficacy not established
≥1 year: 340 mg/m^2/day PO; not to exceed 600 mg/day

2. Acute Lymphoblastic Leukemia
Indicated for treatment of newly diagnosed children with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)
<1 year: Safety and efficacy not established
≥1 year: 340 mg/m^2/day PO; not to exceed 600 mg/day

Dosage Modifications

1. Withhold treatment if fluid retention
2. Hematologic toxicity
   • Generally, discontinue if ANC <1000/mm^3 and/or Plts <50,000/mm^3
   • Resume when ANC >1500/mm^3 and Plts >75,000/mm^3
3. Hepatotoxicity toxicity
   • Withhold if bilirubin >3x ULN or ALT/AST >5x ULN
   • Resume after bilirubin <1.5x ULN and ALT/AST <2.5x ULN at a reduced dose (ie, from 340 mg/m^2/day to 260 mg/m^2/day)
   • Withhold if severe hepatotoxicity; once resolved reduce dose by 25%

Monitor
Monitor patients for GI symptoms at the start of therapy.
Weigh and monitor patients regularly for signs and symptoms of fluid retention.
Carefully monitor patients with cardiac disease or risk factors for cardiac failure, or a history of renal failure. Perform an echocardiogram and determine serum troponin levels in patients with hypereosinophilic syndrome/chronic eosinophilic leukemia and in patients with myelodysplastic/myeloproliferative diseases or aggressive systemic.
Monitor liver function(Transaminases, bilirubin, and alkaline phosphatase) before initiation of treatment and monthly or as clinically indicated.
Monitor thyroid-stimulating hormone in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor the growth of children under imatinib treatment.
Closely monitor patients at risk for tumor lysis Syndrome.
Perform CBCs weekly for the first month, biweekly for the second inonth,and periodically thereafter as clinically indicated.

Cautions
Avoid concomitant strong CYP3A4 inducers -Inhibits CYP 2C9, 2D6, and 3A4 – Fluid retention and edema- Hematologic Toxicity- Cardiovascular Effects- Hepatotoxicity- Hemorrahage- GI effects-Hypereosinophilic cardiac toxicity- Dermatologic effect- Hyperthyroidism- Tumor Lysis Syndrom-Renal impairment – Hepatic Impairment.

Contraindication
Hypersensitivity to any component.

Adverse Effects
>10%
Edema, Neutropenia, Nausea, Muscle cramps, Musculoskeletal pain, Thrombocytopenia, Rash, Fatigue, Diarrhea, Headache, Arthralgia, Abd.Pain ,Myalgia , Nasopharyngitis , Hemorrhage ,Vomiting, Dyspepsia, Cough, Dizziness, URT infection, Fever, Weight Gain, Hepatotoxicity, Insomnia

HOW TO USE
Take with meal and large glass of water
For patients unable to swallow, capsules may be dispersed in water or apple juice the required number of capsules should be placed in the appropriate volume of beverage (50 ml for a 100 mg capsules and 200 ml for a 400 mg capsule) and stirred with a spoon.
Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Patient Information
instruct patients to take imatinib exactly as prescribed and not to change their dose or stop taking Imatinib unless they are told to do so by their health care provider.
Advise patients to take imatinib with a meal and a large glass of water.
Advise women to inform their health care provider if they are or think they may be pregnant.
Advise patients not to breast-feed while taking imatinib.
Advise women of reproductive potential to avoid becoming pregnant while taking this medicine.
Instruct sexually active female patients taking imatinib to use highly effective contraception.
Inform patients to tell their health care provider if they experience adverse reactions during imatinib therapy, including blood in their stool, fever, jaundice, shortness of breath, sudden weight gain, or symptoms of cardiac failure, or if they have a history of cardiac disease or risk factors of cardiac failure.
Advise patients not to take any other medications, including nonprescription medications, such as acetaminophen or herbal products, without talking with their health care provider first. Examples of other medications that patients should not take with imatinib include erythromycin, phenytoin, and warfarin. Also advise patients to tell their health care provider if they are taking or planning to take iron supplements. Also advise patients to avoid grapefruit juice and other foods known to inhibit CYP3A4 while they are taking imatinib. Advise patient not to crush imatinib and to avoid direct contact of capsule ingredients with the skin or mucous membranes. If such contact occurs, advise patient to wash thoroughly.
Inform patients that growth retardation has been reported in children and preadolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children receiving imatinib treatment is recommended. Advise patients that they may experience undesirable effects, such as dizziness, blurred vision, or somnolence, during treatment with imatinib. Therefore, caution patients about driving a car or operating machinery.

OVERDOSE
If overdose is suspected, contact a poison control center or emergency room right away.

MISSED DOSE
If patients miss a dose, instruct them to take their dose as soon as possible, unless it is almost time for their next dose, in which case, instruct them not to take the missed dose. Instruct patients not to take a double dose to make up for any missed doses.

Pregnancy & Lactation
Pregnancy Category: D; postmarket reports of spontaneous abortions and infant congenital anomalies Teratogenic in rats at doses approximating human dose of 800 mg/day that includes exencephaly or encephalocele; absent/reduced frontal and absent parietal bones .
Since this drug can be absorbed through the skin and lungs and may harm an unborn baby, women who are pregnant or who may become pregnant should not handle this medicine or breathe the dust from the capsule.

Lactation: enters breast milk; not recommended.

STORAGE
Store below 30°c, keep away from light and moisture. Do not store in the bathroom. Keep all medications away from children and pets.

Presentation Imatinib
Bottle of 30 Capsules

Reference
BNF 68, part 8.1.5, other antineoplastic drug , page 597-598.
Drug fact, Tyrosine kinase inhibitor ,page 3771-3779.

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