PDR.net

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Gleevec

(Imatinib Mesylate) - Novartis

THERAPEUTIC CLASS

Protein-tyrosine kinase inhibitor

DEA CLASS

RX

INDICATIONS

Treatment of newly diagnosed patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. Adults: Treatment of Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-α therapy. Treatment of relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL). Treatment of myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements. Treatment of aggressive systemic mastocytosis (ASM) patients without the D816V c-Kit mutation or with unknown c-Kit mutational status. Treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) patients 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. Treatment of unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP). Treatment of patients with Kit (CD117)-positive unresectable and/or metastatic malignant GI stromal tumors (GIST). Adjuvant treatment of patients following complete gross resection of Kit (CD117)-positive GIST. Pediatrics: Treatment of newly diagnosed Ph+ ALL in combination with chemotherapy.

ADULT DOSAGE

Adults: CML: Chronic Phase: Usual: 400mg qd. Titrate: May increase to 600mg qd if conditions permit. See PI. Accelerated Phase/Blast Crisis: Usual: 600mg qd. Titrate: May increase to 400mg bid if conditions permit. See PI. Relapsed/Refractory Ph+ ALL: 600mg qd. MDS/MPD; ASM without D816V c-Kit Mutation or with Unknown c-Kit Mutational Status Not Responding Satisfactorily to Other Therapies; HES/CEL: 400mg qd. ASM with Eosinophilia/HES or CEL with FIP1L1-PDGFRα: Initial: 100mg qd. Titrate: May increase to 400mg qd in the absence of adverse reactions and presence of insufficient response. DFSP: 800mg/day (as 400mg bid). Unresectable and/or Metastatic Malignant GIST: Usual: 400mg qd. Titrate: May increase to 400mg bid if signs/symptoms of disease progression at a lower dose are clear and in the absence of severe adverse reactions. Adjuvant Treatment after Complete Gross Resection of GIST: 400mg qd for 3 yrs. Concomitant Strong CYP3A4 Inducers: Avoid concomitant use. If coadministration is necessary, increase dose by at least 50% and carefully monitor response. Severe Hepatic Impairment: Reduce dose by 25%. Moderate Renal Impairment (CrCl 20-39mL/min): Initial: Reduce dose by 50%. Titrate: Increase as tolerated. Max: 400mg. Mild Renal Impairment (CrCl 40-59mL/min): Max: 600mg. Severe Renal Impairment: Use with caution. Hepatotoxicity/Nonhematologic Adverse Reaction: If bilirubin >3X ULN or transaminases >5X ULN, withhold therapy until bilirubin <1.5X ULN and transaminases <2.5X ULN. Continue at reduced dose. Severe Nonhematologic Adverse Reaction: Withhold therapy until the event has resolved. Resume as appropriate, depending on initial severity of event. Neutropenia/Thrombocytopenia: See PI for dosage adjustments. Take with food and a large glass of water.

PEDIATRIC DOSAGE

Pediatrics: ≥1 Yr: Ph+ CML: Usual: 340mg/m^2 qd or split into 2 doses (am and pm). Max: 600mg. Ph+ ALL: Usual: 340mg/m^2 qd. Max: 600mg. Concomitant Strong CYP3A4 Inducers: Avoid concomitant use. If coadministration is necessary, increase dose by at least 50% and carefully monitor response. Severe Hepatic Impairment: Reduce dose by 25%. Moderate Renal Impairment (CrCl 20-39mL/min): Initial: Reduce dose by 50%. Titrate: Increase as tolerated. Max: 400mg. Mild Renal Impairment (CrCl 40-59mL/min): Max: 600mg. Severe Renal Impairment: Use with caution. Hepatotoxicity/Nonhematologic Adverse Reaction: If bilirubin >3X ULN or transaminases >5X ULN, withhold therapy until bilirubin <1.5X ULN and transaminases <2.5X ULN. Reduce dose to 260mg/m^2/day. Severe Nonhematologic Adverse Reaction: Withhold therapy until the event has resolved. Resume as appropriate, depending on initial severity of event. Neutropenia/Thrombocytopenia: See PI for dosage adjustments. Take with food and a large glass of water.

HOW SUPPLIED

Tab: 100mg*, 400mg* *scored

WARNINGS/PRECAUTIONS

Edema and serious fluid retention reported. Hematologic toxicity (eg, anemia/neutropenia/thrombocytopenia) reported; monitor CBCs weekly for 1st month, biweekly for 2nd month, and periodically thereafter as clinically indicated. Severe congestive heart failure (CHF) and left ventricular dysfunction reported; carefully monitor patients with cardiac disease or risk factors for cardiac failure or history of renal failure, and evaluate/treat any patient with cardiac or renal failure. Hepatotoxicity may occur; monitor LFTs before initiation of treatment and monthly, or as clinically indicated. Hemorrhages reported; monitor for GI symptoms at the start of therapy as GI tumor sites may be the source of GI hemorrhages. GI irritation/perforation reported. In patients with HES with occult infiltration of HES cells within the myocardium, cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon initiation of therapy; reversible with administration of systemic steroids, circulatory support measures, and temporarily withholding treatment. Consider echocardiogram and determination of serum troponin in patients with HES/CEL, MDS/MPD or ASM associated with high eosinophil levels; if either is abnormal, consider prophylactic use of systemic steroids (1-2mg/kg) for 1-2 weeks concomitantly at initiation of therapy. Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, reported. May cause fetal harm; sexually active female patients of reproductive potential should use highly effective contraception. Growth retardation reported in children and preadolescents; closely monitor growth. Tumor lysis syndrome (TLS) reported in patients with CML, GIST, ALL, and eosinophilic leukemia; caution in patients at risk of TLS (those with tumors with high proliferative rate or high tumor burden prior to treatment), and correct dehydration and treat high uric acid levels prior to initiation of treatment. May impair mental/physical abilities.

ADVERSE REACTIONS

N/V, edema, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, headache, asthenia, abdominal pain, hemorrhage, malaise, neutropenia, anemia, anorexia.

DRUG INTERACTIONS

See Dosage. Increased levels with CYP3A4 inhibitors; caution with strong CYP3A4 inhibitors (eg, ketoconazole, nefazodone, clarithromycin); avoid with grapefruit juice. Decreased levels with CYP3A4 inducers (eg, rifampin, St. John's wort, enzyme-inducing antiepileptic drugs); consider alternative therapeutic agents with less enzyme induction potential when CYP3A4 inducers are indicated. Increases levels of simvastatin, metoprolol, and CYP3A4 metabolized drugs (eg, dihydropyridine calcium channel blockers, triazolo-benzodiazepines, certain HMG-CoA reductase inhibitors); caution with CYP3A4/CYP2D6 substrates that have a narrow therapeutic window (eg, alfentanil, cyclosporine, ergotamine). Switch from warfarin to low molecular weight or standard heparin if anticoagulation is required during therapy. Inhibits acetaminophen O-glucuronidate pathway in vitro. When concomitantly used with chemotherapy, liver toxicity reported; monitor hepatic function. Hypothyroidism reported in thyroidectomy patients undergoing levothyroxine replacement; closely monitor TSH levels.

PREGNANCY

Category D, not for use in nursing.

MECHANISM OF ACTION

Protein-tyrosine kinase inhibitor; inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Inhibits proliferation and induces apoptosis in bcr-abl-positive cell lines as well as fresh leukemic cells from Ph+ CML. Inhibits the receptor tyrosine kinases for PDGF and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. Inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-Kit mutation, in vitro.

PHARMACOKINETICS

Absorption: Well-absorbed. Absolute bioavailability (98%); T_{max}=2-4 hrs. **Distribution:** Plasma protein binding (95%); found in breast milk. **Metabolism:** Liver via CYP3A4 (major), CYP1A2, CYP2D6, CYP2C9, CYP2C19 (minor); N-demethylated piperazine derivative (major active metabolite). **Elimination:** Feces (68%, 20% unchanged), urine (13%, 5% unchanged); $T_{1/2}$=18 hrs (imatinib), 40 hrs (active metabolite).

ASSESSMENT

Assess for cardiac disease, renal impairment, dehydration, high uric acid levels, pregnancy/nursing status, and possible drug interactions. Perform echocardiogram and determine troponin levels in patients with HES/CEL and with MDS/MPD or ASM associated with high eosinophil levels. Obtain CBCs and LFTs.

MONITORING

Monitor for signs and symptoms of fluid retention, CHF, left ventricular dysfunction, hemorrhage, GI disorders, TLS, bullous dermatologic reactions, and other adverse events. Perform CBCs weekly for the 1st month, biweekly for the 2nd month, and periodically thereafter. Monitor LFTs monthly or as clinically indicated. Monitor growth in children, and TSH levels in thyroidectomy patients undergoing levothyroxine replacement.

PATIENT COUNSELING

Instruct to take drug exactly as prescribed and not to change the dose or to stop taking the medication unless told to do so by physician. Advise women of reproductive potential to avoid becoming pregnant and to notify physician if pregnant. Instruct sexually active females to use highly effective contraception. Instruct not to breastfeed while on therapy. Advise to contact physician if experiencing any side effects during therapy or if patient has a history of cardiac disease or risk factors for cardiac failure. Counsel not to take any other medications, including OTC (eg, herbal products), without consulting physician. Advise that growth retardation has been reported in children and preadolescents, and that growth should be monitored. Caution about driving a car or operating machinery.

ADMINISTRATION/STORAGE

Administration: Oral route. Take with food and a large glass of water. If unable to swallow tab, disperse in a glass of water or apple juice; required number of tab should be placed in the appropriate volume of beverage (approximately 50mL for 100mg tab and 200mL for 400mg tab); stir with a spoon and administer suspension immediately after complete disintegration of tab. Do not crush tab. Avoid direct contact of crushed tab with the skin or mucous membranes; wash thoroughly as outlined in the references if contact occurs. Avoid exposure to crushed tab. **Storage:** 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.