Imatinib

Class: Tyrosine Kinase Inhibitor

Indications:

_Gastrointestinal stromal tumors

_Philadelphia chromosome-positive (Ph+)

_chronic myeloid leukemia (CML) in chronic phase (newly-diagnosed) in children and adults

_Hypereosinophilic syndrome (HES)

_chronic eosinophilic leukemia (CEL)

Available dosage form in the hospital: 100 MG, 400 MG TAB

Trade name: Gleevec

Doses: **Note:** Treatment may be continued until disease progression or unacceptable toxicity. The optimal duration of therapy for chronic myeloid leukemia (CML) in complete remission is not yet determined. Discontinuing CML treatment is not recommended unless part of a clinical trial (Baccarani, 2009; NCCN CML guidelines v.3.2013).

-Ph+ CML: Oral:

-Chronic phase: 400 mg once daily; may be increased to 600 mg daily, if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6-12 months, or loss of previous hematologic or cytogenetic response; a range of up to 800 mg daily is included in the NCCN CML guidelines

***Canadian labeling:* 400 mg once daily; may be increased to 600-800 mg daily

-Accelerated phase or blast crisis: 600 mg once daily; may be increased to 800 mg daily (400 mg twice daily), if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6-12 months, or loss of previous hematologic or cytogenetic response

-Ph+ ALL (relapsed or refractory): Oral: 600 mg once daily

-GIST (adjuvant treatment following complete resection): Oral: 400 mg once daily; recommended treatment duration: 3 years

-GIST (unresectable and/or metastatic malignant): Oral: 400 mg once daily; may be increased up to 800 mg daily (400 mg twice daily), if tolerated, for disease progression. **Note:** Significant improvement (progression-free survival, objective response rate) was demonstrated in patients with KIT exon 9 mutation with 800 mg (versus 400 mg), although overall survival (OS) was not impacted. The higher dose did not demonstrate a difference in time to progression or OS patients with Kit exon 11 mutation or wild-type status

***Canadian labeling:* 400-600 mg daily (depending on disease stage/progression); may be increased to 600-800 mg daily

-ASM with eosinophilia: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) for insufficient response to lower dose

-ASM without D816V c-Kit mutation or c-Kit mutation status unknown: Oral: 400 mg once daily

-DFSP: Oral: 400 mg twice daily

-HES/CEL: Oral: 400 mg once daily

-HES/CEL with FIP1L1-PDGFRα fusion kinase: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) if insufficient response to lower dose

-MDS/MPD: Oral: 400 mg once daily

-Ph+ ALL (induction, newly diagnosed): *Canadian labeling (not an approved use in the U.S.):* Oral: 600 mg once daily

-Chordoma, progressive, advanced, or metastatic expressing PDGFRB and/or PDGFB (unlabeled use): Oral: 400 mg twice daily

-Desmoid tumors, unresectable and/or progressive (unlabeled use): Oral: 300 mg twice daily (BSA ≥1.5 m^2), 200 mg twice daily (BSA 1-1.49 m^2), 100 mg twice daily (BSA <1 m^2) **or** 400 mg once daily; may increase to 400 mg twice daily if progressive disease on 400 mg daily

-Melanoma, advanced or metastatic with C-KIT mutation (unlabeled use): Oral: 400 mg twice daily

-Stem cell transplant (SCT, unlabeled use) for CML (in patients who have not failed imatinib therapy prior to transplant): Oral:

-Prophylactic use to prevent relapse post SCT: 400 mg daily starting after engraftment for 1 year post transplant or 300 mg daily starting on day +35 post SCT (increased to 400 mg within 4 weeks) and continued until 12 months post transplant

-Relapse post SCT: Initial: 400 mg daily; if inferior response after 3 months, dose may be increased to 600-800 mg daily or 400-600 mg daily (chronic phase) **or** 600 mg daily (blast or accelerated phase)

Geriatric
Refer to adult dosing.

Renal Impairment:
***U.S. labeling:*

- Mild impairment (Cl_{cr} 40-59 mL/minute): Maximum recommended dose: 600 mg.
- Moderate impairment (Cl_{cr} 20-39 mL/minute): Decrease recommended starting dose by 50%; dose may be increased as tolerated; maximum recommended dose: 400 mg.
- Severe impairment (Cl_{cr} <20 mL/minute): Use caution; a dose of 100 mg daily has been tolerated in a limited number of patients with severe impairment (Gibbons, 2008).

***Canadian labeling:*

- Mild impairment (Cl_{cr} 40-59 mL/minute): Initial dose: 400 mg once daily (minimum effective dose); titrate to efficacy and tolerability.

- Moderate impairment (Cl_{cr} 20-39 mL/minute): Initial dose: 400 mg once daily (minimum effective dose); titrate to efficacy and tolerability; the use of 800 mg dose is not recommended.

- Severe impairment (Cl_{cr} <20 mL/minute): Use is not recommended.

Hepatic Impairment:

***U.S. labeling:*

- Mild-to-moderate impairment: No dosage adjustment necessary.
- Severe impairment: Reduce dose by 25%.

***Canadian labeling:*

- Mild-to-moderate impairment: Initial dose: 400 mg once daily (minimum effective dose).
- Severe impairment: Initial dose: 200 mg once daily; may increase up to 300 mg once daily in the absence of severe toxicity; decrease dose with unacceptable toxicity.

Dosage adjustment for hepatotoxicity (during therapy): If elevations of bilirubin >3 times ULN or transaminases >5 times ULN occur, withhold treatment until bilirubin <1.5 times ULN and transaminases <2.5 times ULN. Resume treatment at a reduced dose as follows (**Note:** The decision to resume treatment should take into consideration the initial severity of hepatoxicity):

- If current dose 400 mg daily, reduce dose to 300 mg daily
- If current dose 600 mg daily, reduce dose to 400 mg daily
- If current dose 800 mg daily, reduce dose to 600 mg daily

Dosing: Adjustment for Toxicity

1. Hematologic toxicity:

-Chronic phase CML (initial dose 400 mg daily in adults or 340 mg/m^2/day in children); ASM, MDS/MPD, and HES/CEL (initial dose 400 mg daily); or GIST (initial dose 400 mg daily [U.S. labeling] or 400-600 mg daily [Canadian labeling]): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at original starting dose. For recurrent neutropenia and/or thrombocytopenia, withhold until recovery, and reinstitute treatment at a reduced dose as follows:

- If initial dose 400 mg daily, reduce dose to 300 mg daily.
- If initial dose 600 mg daily (Canadian labeling; not in U.S. labeling), reduce dose to 400 mg daily.

-CML (accelerated phase or blast crisis) and Ph+ ALL: Adults (initial dose 600 mg daily): If ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L, establish whether cytopenia is related to leukemia (bone marrow aspirate or biopsy). If unrelated to leukemia, reduce dose to 400 mg daily. If cytopenia persists for an additional 2 weeks, further reduce dose to 300 mg daily. If cytopenia persists for 4 weeks and is still unrelated to leukemia, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L, then resume treatment at 300 mg daily.

-ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase: Adults (starting dose 100 mg daily): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at previous dose.

-DFSP: Adults (initial dose 800 mg daily): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L, withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at reduced dose of 600 mg daily. For recurrent neutropenia and/or thrombocytopenia, withhold until recovery, and reinstitute treatment with a further dose reduction to 400 mg daily.

2. Nonhematologic toxicity (eg, severe edema): Withhold treatment until toxicity resolves; may resume if appropriate (depending on initial severity of adverse event).

Common side effect:

Cardiovascular: Edema/fluid retention (11% to 86%; grades 3/4: 3% to 13%; includes aggravated edema, anasarca, ascites, pericardial effusion, peripheral edema, pulmonary edema, and superficial edema); facial edema (≤17%), chest pain (7% to 11%), hypotension (Ph+ ALL [pediatric] grades 3/4: 11%)

Central nervous system: Fatigue (29% to 75%), pain (≤47%), fever (6% to 41%), headache (8% to 37%), dizziness (5% to 19%), insomnia (10% to 15%), depression (≤15%), anxiety (8% to 12%), chills (≤11%)

Dermatologic: Rash (9% to 50%; grades 3/4: 1% to 9%), dermatitis (GIST ≤39%), pruritus (8% to 26%), alopecia (GIST 10% to 15%)

Endocrine & metabolic: LDH increased (GIST ≤60%), hypokalemia (6% to 13%; Ph+ ALL [pediatric] grades 3/4: 34%), hypoproteinemia (≤32%), albumin decreased (≤21%; grade 3: ≤4%)

Gastrointestinal: Nausea (42% to 73%; Ph+ ALL [pediatric] grades 3/4: 16%), diarrhea (25% to 59%; Ph+ ALL [pediatric] grades 3/4: 9%), vomiting (11% to 58%), abdominal pain (3% to 57%), anorexia (≤36%), weight gain (5% to 32%), dyspepsia (11% to 27%), flatulence (≤25%), abdominal distension (≤19%), stomatitis/mucositis (≤10% to 16%), constipation (9% to 16%), taste disturbance (≤13%)

Hematologic: Anemia (25% to 80%; grade 3: 1% to 42%; grade 4: ≤11%), leukopenia (GIST 5% to 47%; grades 3/4: 2%), hemorrhage (3% to 53%; grades 3/4: ≤19%), neutropenia (12% to 16%, grade 3: 7% to 27%; grade 4: 3% to 48%), thrombocytopenia (grade 3: 1% to 31%; grade 4: <1% to 33%)

Hepatic: Transaminases and/or bilirubin increased (Ph+ ALL [pediatric] grades 3/4: 57%), AST increased (≤38%; grade 3: 2% to 5%; grade 4: ≤3%), ALT increased (≤34%; grade 3: 2% to 7%; grade 4: <3%), alkaline phosphatase increased (≤17%; grade 3: ≤6%; grade 4: <1%), bilirubin increased (≤13%; grade 3: 1% to 4%; grade 4: ≤3%)

Neuromuscular & skeletal: Muscle cramps (16% to 62%), arthralgia (≤40%), musculoskeletal pain (children 21%; adults 38% to 49%), myalgia (9% to 32%), joint pain (11% to 31%), weakness (≤21%), rigors (10% to 12%), paresthesia (≤12%), bone pain (≤11%)

Ocular: Periorbital edema (29% to ≤74%), lacrimation increased (DFSP 25%; GIST ≤18%), blurred vision (≤11%)

Renal: Serum creatinine increased (≤44%; grade 3: ≤3%; DFSP: grade 4: 8%)

Respiratory: Nasopharyngitis (1% to 31%), cough (11% to 27%), dyspnea (≤21%), upper respiratory tract infection (3% to 21%), pharyngolaryngeal pain (≤18%), rhinitis (DFSP 17%), pharyngitis (CML 10% to 15%), pneumonia (CML 4% to 13%), sinusitis (4% to 11%)

Pregnancy category: D