

DRUG NAME: Imatinib**SYNONYM(S):** STI-571, imatinib mesylate**COMMON TRADE NAME(S):** GLEEVEC®, GLIVEC®**CLASSIFICATION:** tyrosine kinase inhibitor*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Imatinib inhibits BCR-ABL tyrosine kinase, the fusion protein created by the Philadelphia chromosome abnormality that characterizes chronic myeloid leukemia. Competitive inhibition at the enzyme's ATP-binding site leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction.¹ Inhibition is not completely selective as imatinib also inhibits the receptor tyrosine kinases for platelet-derived growth factor and c-Kit, a stem cell factor.² Cells that express BCR-ABL undergo growth inhibition or apoptosis but normal cells are not affected.^{1,2}

PHARMACOKINETICS:

| | | |
|--------------------------|---|--|
| Interpatient variability | 40% for clearance | |
| Oral Absorption | 98% mean absolute bioavailability; not affected by fatty food ³ | |
| | time to peak plasma concentration | 2-4 h |
| Distribution | extensively bound to plasma protein | |
| | cross blood brain barrier? | animal studies showed poor penetration ⁴ |
| | volume of distribution | ~ 295 L ⁵ |
| | plasma protein binding | 95%, mostly to albumin and α_1 -acid glycoprotein |
| Metabolism | 75%, primarily oxidative ⁶ via CYP3A4/5; main active metabolite is equipotent to imatinib. Other CYP450 enzymes (1A2, 2D6, 2C9, 2C19) have a minor role. | |
| | active metabolite(s) | N-desmethyl derivative (CGP 74588) ⁶ |
| | inactive metabolite(s) | none known |
| Excretion | fecal and urinary excretion | |
| | urine | 13% over 7 days |
| | feces | 68% over 7 days |
| | terminal half life | imatinib: 18 h CGP 74588: 40 h |
| | clearance | 13-17 L/h ⁵ |
| Gender | no clinically significant difference ⁷ | |
| Elderly | small effect of age on the volume of distribution (12% increase in patients > 65 years old); not clinically significant ⁷ | |
| Children | no clinically significant difference | |

Adapted from reference² unless specified otherwise.**USES:****Primary uses:***leukemia, chronic myeloid (CML)^{2,8}*sarcoma, gastrointestinal stromal tumour (GIST)¹³

*Health Canada Therapeutic Products Programme approved indication

Other uses:leukemia, acute (Ph+)^{9-12,11}

SPECIAL PRECAUTIONS:**Contraindications:**

- history of hypersensitivity reaction to imatinib²
- pregnancy^{14,15}

Caution:

- Longterm treatment may result in a **progressive loss of renal function** over time; monitor renal function prior to treatment and periodically thereafter.^{14,16}
- **Reactivation of Hepatitis B virus** (HBV) has sometimes occurred in chronic carriers of HBV after receiving BCR-ABL tyrosine kinase inhibitors; test for HBV infection prior to treatment and monitor for signs of active HBV infection.¹⁷

Carcinogenicity: Carcinoma was seen at doses of 30-60 mg/kg/day in an animal carcinogenicity study. No significant increase in second malignancies was seen in clinical trials.¹⁸

Mutagenicity: Imatinib was not mutagenic in the Ames test and mammalian *in vitro* mutation test. Two intermediates of the manufacturing process, which are present in the final product, are mutagenic in the Ames test. Imatinib is clastogenic in mammalian *in vitro* tests.²

Fertility: Effects on male fertility have not been studied in patients. There is clinical evidence of both profound oligospermia and maintained male fertility as well as pre-clinical evidence of impaired spermatogenesis also without reduced fertility.¹⁴ No information was found with regards to female fertility.

Pregnancy: Spontaneous abortions and congenital anomalies have been reported by women taking imatinib during pregnancy. In animal studies, dose dependent embryo-fetal toxicity and/or teratogenicity (exencephaly, encephalocele, and absent or reduced frontal, parietal, and/or intraparietal bones) have been observed in rats, but not in rabbits. For women of childbearing potential, a serum or urine pregnancy test is recommended to confirm that female patients are not pregnant prior to treatment with imatinib. Effective contraception should be used during treatment.¹⁴

Breastfeeding is not recommended because an amount equivalent to 30% of the maternal dose per unit body weight has been found in breast milk in animal studies.²

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

| ORGAN SITE | SIDE EFFECT |
|---|--|
| Clinically important side effects are in bold, italics | |
| blood/bone marrow febrile neutropenia | <i>anemia</i> ; newly diagnosed CML and GIST (severe 3-4%); CML accelerated phase and blast crisis (severe 40-50%) |
| | anemia, hemolytic (rare) ^{19,20} ; generally occurs within 1-4 weeks ²⁰ |
| | bone marrow necrosis (<1%); generally occurs within 1-4 weeks ²¹ |
| | myelodysplasia (<1%); generally occurs after more than 3 months ^{22,23} |
| | <i>neutropenia</i> ; newly diagnosed CML and GIST (severe 8-13%); CML accelerated phase and blast crisis (severe 58-63%); median duration 2-3 weeks |
| | splenic rupture (<1%); generally occurs after more than 1-3 months ²⁴ |

| ORGAN SITE | SIDE EFFECT |
|---|--|
| Clinically important side effects are in bold, italics | |
| | thrombocytopenia (severe 17-58%); newly diagnosed CML and GIST (severe 1-7%) CML accelerated phase and blast crisis (severe 40-50%); median duration 3-4 weeks |
| cardiovascular (general) | cardiac tamponade (<1%); generally occurs after more than 3 months ²⁵ |
| | congestive heart failure (<1%); generally occurs after 7 months ²⁶ |
| | edema (52-68%, severe 2-10%); more common in \geq 65 years old |
| constitutional symptoms | fatigue (24-33%, severe 0-3%) |
| | fever (14-38%, severe 1-7%) |
| | night sweats (8-10%, severe 0-1%) |
| | weakness (5-10%, severe 0-3%) |
| | weight gain (1-4%, severe 0-2%) |
| dermatology/skin | cutaneous reactions, severe (<1%) ^{20,27-45} |
| | photosensitivity (<1%) ²⁸ |
| | pruritus (6-10%, severe 0-1%) |
| | rash (32-39%, severe 3-4%) |
| gastrointestinal | <i>emetogenic potential</i> : low moderate |
| | anorexia (3-14%, severe 0-2%) |
| | constipation (4-13%, severe \leq 1%) |
| | diarrhea (33-39%, severe 3-4%) |
| | diverticulitis (\leq 1%) ¹⁸ |
| | gastrointestinal perforation (< 1%) ¹⁸ |
| | nausea (55-68%, severe 2-5%) |
| | vomiting (28-49%, severe 1-3%) |
| endocrine | gynecomastia (\leq 1%) ²⁸ ; generally occurs after more than 3 months ⁴⁶ |
| hemorrhage | bleeding episode (13-48%, severe 8-16%) |
| | CNS bleeding (\leq 4%, severe 0-2%) |
| | epistaxis (3-12%, severe 0-3%) |
| | gastrointestinal bleeding (\leq 5%, severe 0-3%) |
| | petechiae (1-10%, severe 0-1%) |
| hepatic | elevated bilirubin (severe 0-4%) |
| | elevated ALT, AST, alkaline phosphatase (severe 1-6%) |
| | hepatic necrosis, early to delayed (<1%); generally occurs after more than 1-3 months ^{47,48} |
| infection | pneumonia (1-10%, 0-5%) |
| | varicella-zoster virus infection (2%); generally occurs after 1-3 months ⁴⁹ |
| metabolic/laboratory | hypokalemia (2-12%, severe 0-3%) |
| musculoskeletal | arthralgia (21-26%, severe 1-5%) |
| | avascular necrosis/hip necrosis (<1%) ¹⁸ |

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in bold, italics | |
| | muscle cramps (25-46%, severe <1%) |
| | myalgia (7-18%, severe 0-2%) |
| ocular/visual | periorbital edema ² (70%, rarely severe) ⁵⁰⁻⁵² ; generally occurs after more than 1-3 months ^{51,52} |
| | watery eye (12%) ⁵⁰ |
| pain | abdominal pain (20-23%, severe 0-5%) |
| | headache (24-28%, severe 0-4%) |
| | pain (27-39%, severe 1-8%) |
| pulmonary | cough (9-22%, severe 0-1%) |
| | dyspnea (5-12%, severe 0-5%) |
| | pneumonitis (<1%) ^{28,53-55} ; generally occurs within 1-3 months ^{54,55} |
| | pleural effusions (<1%) ^{28,56} |
| | pulmonary alveolar proteinosis (<1%); generally occurs after more than 1-3 months ⁵⁷ |
| renal/genitourinary | nasopharyngitis (5-10%, severe 0-1%) |
| | elevated creatinine (severe ≤1%) |
| | renal failure, acute (<1%) ^{58,59} ; may occur after one week ⁵⁸ to two months ⁵⁹ renal dysfunction, progressive^{14,16}; loss of function may be greatest in first year, may contribute to development or worsening of some kidney diseases |
| syndromes | tumour lysis syndrome (<1%); generally occurs within 4-5 days ^{60,61} |

Adapted from reference² unless specified otherwise.

Bone marrow suppression, especially neutropenia and thrombocytopenia, is more common at higher doses (≥ 750 mg/day) and in blast crisis or accelerated phase compared to chronic phase when treating chronic myeloid leukemia. Management is dose reduction, interruption or (rarely) discontinuation of imatinib.² Filgrastim at a dose of 300-480 mcg two to three times weekly^{62,63} or daily⁶⁴ has also been used.

Edema is usually mild to moderate and most frequently periorbital or in lower limbs but may include pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema.² Serious or life threatening edema has rarely been reported, including periorbital edema,^{51,52} intramuscular edema,⁶⁵ and cerebral edema.⁶⁶ It appears to be dose related (especially ≥ 600 mg/day) and is more common in the elderly and female patients.² Edema may be due to inhibition of platelet-derived growth factor receptor which regulates interstitial fluid pressure. Onset varies from weeks to months.^{51,52,65,66} Management is largely symptomatic with diuretics, other supportive measures or imatinib dose reduction.²

Hepatotoxicity with severe elevations of transaminases or bilirubin may be life threatening. Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Management of hepatotoxicity is dose reduction, interruption (median duration one week) or discontinuation (<0.5%) of imatinib.²

Hepatitis B virus (HBV) reactivation has been reported in chronic HBV carriers and patients with a documented history of hepatitis B after receiving BCR-ABL inhibitors. Increased viral load or positive serology may occur with HBV reactivation. Some cases have included acute hepatic failure or fulminant hepatitis leading to liver transplantation or death. The mechanism and frequency of HBV reactivation is not known but may occur at any time during treatment, and is considered a class effect of the BCR-ABL TKIs. Test for HBV infection prior to treatment and monitor for symptoms of active HBV infection during treatment and for several months after termination of treatment.¹⁷

Severe skin reactions are rare and varied in presentations,^{27,28} including exanthematous (erythematous) reactions,²⁸⁻³² erythroderma and exfoliative dermatitis,^{20,28,32,33} eruptions,^{28,34-37} pigmentation reactions,^{28,38-41} photosensitisation,^{28,40} hemorrhagic blisters,^{42,43} and inflammation of subcutaneous fat tissue⁴⁴ and blood vessels.³² The onset is variable and may be early,^{30,32,45} delayed³⁸⁻⁴¹ or late.³⁸⁻⁴¹ The median onset was about 1-2 months^{30,32,45} but may be more delayed with pigmentation changes^{38,39,41} and photosensitisation.⁴⁰ Skin biopsies tended to show infiltration of inflammatory cells^{27,32,39,45} and reactions seemed to be dose-related.^{27,32,39,45,67} Management is largely symptomatic, including discontinuation or reduction of dose, oral and/or topical corticosteroids, antihistamines and immunosuppressants.^{27,30,32,39,45,64,67}

INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|--|--|--|---|
| grapefruit or grapefruit juice ⁶⁸ | may increase plasma level of imatinib | may inhibit CYP3A4 metabolism of imatinib in the intestinal wall | avoid grapefruit and grapefruit juice |
| ketoconazole ⁶⁸ | increases plasma level of imatinib | inhibits CYP 3A4 metabolism of imatinib | use with caution |
| levothyroxine ⁶⁹ | imatinib may increase thyroid-stimulating hormone level and symptoms of hypothyroidism | imatinib may increase hepatic clearance of levothyroxine | closely monitor thyroid function during concurrent use and adjust levothyroxine dose as needed |
| rifampin | decreases plasma level of imatinib | induces CYP3A4 metabolism of imatinib | avoid concurrent use |
| simvastatin | increases plasma level of simvastatin | inhibits CYP3A4 metabolism of simvastatin | avoid concurrent use |
| warfarin | prolongs bleeding time | possibly inhibits CYP2C9 and CYP3A4 metabolism of warfarin | closely monitor bleeding parameters during concurrent use and adjust warfarin dose as needed, or consider other alternatives (eg, low-molecular weight or standard heparin) |

Adapted from reference² unless specified otherwise.

Imatinib may increase plasma concentrations of other CYP3A4 metabolised drugs (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors).²⁸

CYP3A4 inhibitors may decrease metabolism and increase imatinib plasma concentrations. Concurrent administration of drugs that inhibit CYP3A4 (eg, clarithromycin, erythromycin, grapefruit juice, itraconazole) may significantly increase exposure of imatinib.²⁸ Drugs that have high oral bioavailability (eg, >0.7) are less likely to be affected by grapefruit juice.

CYP3A4 inducers may increase metabolism and decrease imatinib plasma concentrations. Concurrent administration of drugs that induce CYP3A4 (eg, carbamazepine, dexamethasone, phenytoin, phenobarbital, St. John's Wort) may significantly reduce exposure of imatinib.²⁸

Imatinib may increase systemic exposure to acetaminophen, at therapeutic doses, through inhibition of acetaminophen O-glucuronidation. Human studies have not been performed, but caution is recommended when using imatinib and acetaminophen concurrently.⁷⁰

SUPPLY AND STORAGE:

Tablets: 100 mg, 400 mg; store at room temperature.¹⁸

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

| | |
|--|---|
| Oral: | <i>400-600 mg (range 400-800mg) PO once daily.</i> Administer with food. ² 800 mg dose should be administered in two divided doses. ²⁸ |
| Dosage in myelosuppression ²⁸ : | <u>CML chronic phase or GIST</u> If ANC < 1 x10 ⁹ /L or platelet < 50 x10 ⁹ /L, hold until ANC ≥ 1.5 and platelets ≥ 75: <ul style="list-style-type: none"> • <i>CML</i>: if 1st episode, restart at 400 mg daily; if 2nd episode, restart at 300 mg daily (dosages < 300 mg/day not recommended as they were found to be ineffective in early studies) • <i>GIST</i>: if 1st episode, restart at 600 mg daily; if 2nd episode, restart at 400 mg daily <u>CML accelerated phase or blast crisis</u> If ANC < 0.5 x10 ⁹ /L or platelet < 10 x10 ⁹ /L and <ul style="list-style-type: none"> • <i>cytopenia unrelated to disease</i>: reduce from 600 mg to 400 mg daily • <i>cytopenia persists for 2 weeks</i>: reduce further to 300 mg daily • <i>cytopenia persists for 4 weeks</i>: hold until ANC ≥ 1 and platelets ≥ 20 and then restart 300 mg daily |
| Dosage in renal failure: | no adjustment required |
| Dosage in hepatic failure ^{28,71} : | If bilirubin > 3 x ULN or ALT/AST > 5 x ULN: <ul style="list-style-type: none"> • hold until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN • restart at 300 mg (reduced from 400 mg) or 400 mg (reduced from 600 mg) • full dose had been used in four patients with severe jaundice^{72,73} |
| Dosage in dialysis: | no information found |
| <u>Children:</u> | |
| Oral: | 260 mg/m ² once daily or split daily into two (once in the morning and once in the evening) ²⁸ Administer with food. ²⁸ |
| Dosage in myelosuppression ²⁸ : | <u>CML chronic phase</u> If ANC < 1 x10 ⁹ /L or platelet < 50 x10 ⁹ /L, hold until ANC ≥ 1.5 and platelets ≥ 75: <ul style="list-style-type: none"> • If 1st episode, restart at 260 mg/m² daily. • If 2nd episode, restart at 200 mg/m² daily. |
| Dosage in hepatic failure ^{28,71} : | If bilirubin > 3 x ULN or ALT/AST > 5 x ULN: <ul style="list-style-type: none"> • hold until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN • restart at 200 mg/m² daily (reduced from 260 mg/m² daily) or 260 mg/m² daily (reduced from 340 mg/m² daily) |

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