DRUG NAME: IMATINIB

SYNONYM(S): STI-571, imatinib mesylate

COMMON TRADE NAME(S): GLEEVEC®, GLIVEC®

CLASSIFICATION: tyrosine kinase inhibitor, cytotoxic

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. The 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	
Ethnicity	no information found	

Adapted from reference 2 unless specified otherwise.

USES:

Primary uses:
*leukemia, chronic myeloid (CML)[2,8]
*sarcoma, gastrointestinal stromal tumour (GIST)[13]

Other uses:
leukemia, acute (Ph+)[9-12]

*Health Canada Therapeutic Products Programme approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to imatinib.[2]

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.[14]

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: Studies in animals have shown decreased fertility.[2]

Pregnancy: FDA Pregnancy Category D.[2] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

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:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow febrile neutropenia	***anemia*** newly diagnosed CML and GIST: severe 3-4% CML accelerated phase and blast crisis: severe 40-50%
	anemia, hemolytic (rare)[15,16]; generally occurs within 1-4 weeks[16]
	bone marrow necrosis (< 1%); generally occurs within 1-4 weeks[17]
	myelodysplasia (< 1%); generally occurs after more than 3 months[18,19]
	neutropenia 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[20]
	thrombocytopenia (severe 17-58%) newly diagnosed CML and GIST: severe 0.7-7% 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[21]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	congestive heart failure (<1%); generally occurs after 7 months[22]
	edema, more common in ≥ 65 years old (52-68%, severe 2-10%)
constitutional symptoms	fatigue (24-33%, severe 0.2-3%)
	fever (14-38%, severe 1-7%)
	night sweats (8-10%, severe ≤1%)
	weakness (5-10%, severe 0.2-3%)
	weight gain (1-4%, severe 0.4-2%)
dermatology/skin	cutaneous reactions, severe (< 1%)[16,23-41]
	photosensitivity (0.1-1%)[24]
	pruritus (6-10%, severe ≤1%)
	rash (32-39%, severe 3-4%)
gastrointestinal	*emetogenic potential:* low moderate
	anorexia (3-14%, severe 0-2%)
	constipation (4-13%, severe ≤1%)
	diarrhea (33-39%, severe 3-4%)
	diverticulitis (< 1%)[14]
	gastrointestinal perforation (< 1%)[14]
	nausea (55-68%, severe 2-5%)
	vomiting (28-49%, severe 0.9-3%)
endocrine	gynecomastia (0.1-1%)[24]; generally occurs after more than 3 months[42]
hemorrhage	bleeding episode (13-48%, severe 8-16%)
	CNS bleeding (0.4-4%, severe 0.4-2%)
	epistaxis (3-12%, severe 0-3%)
	gastrointestinal bleeding (0.2-5%, severe <3%)
	petechiae (0.9-10%, severe ≤1%)
hepatic	***elevated bilirubin*** (severe 0.4-3.5%)
	elevated ALT, AST, alkaline phosphatase (severe 1.1-5.5%)
	hepatic necrosis, early to delayed (< 1%); generally occurs after more than 1-3 months[43,44]
infection	pneumonia (1-10%, 0-5%)
	varicella-zoster virus infection (2%); generally occurs after 1-3 months[45]
metabolic/laboratory	hypokalemia (2-12%, severe 0-3%)
musculoskeletal	arthralgia (21-26%, severe 0.8-5%)
	avascular necrosis/hip necrosis (< 1%)[14]
	muscle cramps (25-46%, severe <1%)
	myalgia (7-18%, severe 0-2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
ocular/visual	periorbital edema[2] (70%, rarely severe)[46-48]; generally occurs after more than 1-3 months[47,48]
	watery eye (12%)[46]
pain	abdominal pain (20-23%, severe 0.2-5%)
	headache (24-28%, severe 0.2-4%)
	pain (27-39%, severe 1-8%)
pulmonary	cough (9-22%, severe <1%)
	dyspnea (5-12%, severe 0.2-5%)
	pneumonitis (< 1%)[24,49-51]; generally occurs within 1-3 months[50,51]
	pleural effusions (< 1%)[24,52]
	pulmonary alveolar proteinosis (< 1%); generally occurs after more than 1-3 months[53]
	nasopharyngitis (5-10%, severe 0.2%)
renal/genitourinary	elevated creatinine (severe ≤1.2%)
	renal failure, acute (< 1%)[54,55]; may occur after one week[54] to two months[55]
syndromes	tumour lysis syndrome (< 1%) ; generally occurs within 4-5 days[56,57]

Adapted from reference 2 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[58,59] or daily[60] 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,[47,48] intramuscular edema,[61] and cerebral edema.[62] 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.[47,48,61,62] 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]

Severe skin reactions are rare and varied in presentations,[23,24] including exanthematous (erythematous) reactions,[24-28] erythroderma and exfoliative dermatitis,[16,24,28,29] eruptions,[24,30-33] pigmentation reactions,[24,34-37] photosensitisation,[24,36] hemorrhagic blisters,[38,39] and inflammation of subcutaneous fat tissue[40] and blood vessels.[28] The onset is variable and may be early,[26,28,41] delayed[34-37] or late.[34-37] The median onset was about 1-2 months[26,28,41] but may be more delayed with pigmentation changes[34,35,37] and photosensitisation.[36] Skin biopsies tended to show infiltration of inflammatory cells [23,28,35,41] and reactions seemed to be dose-related.[23,28,35,41,63] Management is largely symptomatic, including discontinuation or reduction of dose,oral and/or topical corticosteroids, antihistamines and immunosuppressants.[23,26,28,35,41,60,63]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit or grapefruit juice[64]	may increase plasma level of imatinib	may inhibit CYP3A4 metabolism of imatinib in the intestinal wall	avoid grapefruit and grapefruit juice
ketoconazole[64]	increases plasma level of imatinib	inhibits CYP 3A4 metabolism of imatinib	use with caution
levothyroxine[65]	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 reference 2 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).[24]

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.[24] 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.[24]

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.[66]

SUPPLY AND STORAGE:

Tablets: 100 mg, 400 mg; store at room temperature.[14]

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:

400-600 mg (range 400-800mg) PO once daily.
Administer with food.[2] 800 mg dose should be administered in two divided doses.[24]

Dosage in myelosuppression[24]:

CML chronic phase or GIST
If ANC < 1 $x10^9$/L or platelet < 50 $x10^9$/L, hold until ANC ≥ 1.5 and platelets ≥ 75:

- *CML*: 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)
- *GIST*: if 1st episode, restart at 600 mg daily; if 2nd episode, restart at 400 mg daily

CML accelerated phase or blast crisis
If ANC < 0.5 $x10^9$/L or platelet < 10 $x10^9$/L and

- *cytopenia unrelated to disease*: reduce from 600 mg to 400 mg daily
- *cytopenia persists for 2 weeks*: reduce further to 300 mg daily
- *cytopenia persists for 4 weeks*: hold until ANC ≥ 1 and platelets ≥ 20 and then restart 300 mg daily

Dosage in renal failure:

no adjustment required

Dosage in hepatic failure[24,67]:

If bilirubin > 3 x ULN or ALT/AST > 5 x ULN:

- 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[68,69]

Dosage in dialysis:

no information found

Children:

Oral:

260 mg/m^2 once daily or split daily into two (once in the morning and once in the evening)[24]

Administer with food.[24]

Dosage in myelosuppression[24]:

CML chronic phase
If ANC < 1 $x10^9$/L or platelet < 50 $x10^9$/L, hold until ANC ≥ 1.5 and platelets ≥ 75:

- If 1st episode, restart at 260 mg/m^2 daily.
- If 2nd episode, restart at 200 mg/m^2 daily.

Dosage in hepatic failure[24,67]:

If bilirubin > 3 x ULN or ALT/AST > 5 x ULN:

- hold until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN
- restart at 200 mg/m^2 daily (reduced from 260 mg/m^2 daily) or 260 mg/m^2 daily (reduced from 340 mg/m^2 daily)

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