Drug Monograph

A - Drug Name

iMAtinib

COMMON TRADE NAME(S): Gleevec®

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B - Mechanism of Action and Pharmacokinetics

Imatinib is an inhibitor of multiple tyrosine kinases including c-Kit, Abl, SCF and PDGFR. Imatinib may thus be active in diseases where these are mutated, constitutively activated, have fusion proteins or dysregulated pathways, such as Philadelphia chromosome positive leukemia, GIST, myelodysplastic syndromes and some sarcomas. The Philadelphia chromosome, characteristic of chronic myelogenous leukemia (CML), is created by a reciprocal translocation between chromosomes 9 and 22, and results in production of a constitutively activated kinase (Bcr-Abl tyrosine kinase).

Absorption	Bioavailability	98%
	Effects with food	High fat meals reduce absorption (11%) and exposure (7.4 %), but not clinically significant.
Distribution	Imatinib has a linear and dose-dependent pharmacokinetic profile. Daily dosing leads to a 1.5-2.5 fold accumulation at steady state. Body weight and gender do not appear to affect imatinib pharmacokinetics	
	Cross blood brain barrier?	No information found (unlikely)
	PPB	95% (albumin, α_1-acid glycoprotein)

Metabolism	Imatinib is mainly metabolized by the CYP3A4 enzyme; other cytochrome P450 iso-enzymes (CYP1A2, CYP2D6, CYP2C9, CYP2C19) play minor roles in the metabolism of imatinib.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Imatinib is eliminated predominantly by fecal excretion (68%) and in urine (13%) within 7 days.	
	Half-life	18 hours

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C - Indications and Status

Health Canada Approvals:

- Chronic myeloid leukemia (CML)
- Acute lymphoblastic leukemia (ALL)
- Aggressive systemic mastocytosis (ASM) and Systemic mastocytosis with an associated clonal hematological non-mast-cell disorder (SM-AHNMD)
- Dermatofibrosarcoma protuberans (DFSP)
- Myelodysplastic / myeloproliferative diseases (MDS/MPD)
- Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL)
- Gastrointestinal stromal tumours (GIST)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table contains adverse effects and incidences reported in newly diagnosed CML patients. Also includes rare side effects reported in post-marketing and other clinical studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	E
	Pericarditis , tamponade (rare)	E
	Pulmonary hypertension (rare)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (5%)	E
	Hand-foot syndrome (1%)	E
	Photosensitivity (<10%)	E
	Rash (40%) (may be severe)	E
Gastrointestinal	Abdominal pain (37%)	E
	Anorexia (7%)	E D
	Constipation (11%)	E
	Diarrhea (45%)	E
	Dyspepsia (19%)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Nausea, vomiting (50%)	I
General	Fatigue (39%)	I E
	Fluid retention (including effusions) (62%)	E D
	Flu-like symptoms (18%)	I E
Hematological	Hemorrhage (including CNS, GI hemorrhage)	E
	Myelosuppression ± infection, bleeding (grade 3 and 4: 17%, may be severe)	E
Hepatobiliary	↑ LFTs (12%) (may be severe)	E D
	Pancreatitis (<1%)	E
Hypersensitivity	DRESS syndrome (rare)	E
	Hypersensitivity (rare)	I
Infection	Infection (31%) (including opportunistic and atypical infections; HBV reactivation)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (24%)	E
	Hypothyroidism (rare)	D
	Tumour lysis syndrome (rare)	I E

Musculoskeletal	Avascular necrosis (rare)	E
	Musculoskeletal pain (50%) (includes withdrawal syndrome)	E
	Osteonecrosis (rare)	D L
	Rhabdomyolysis (or myopathy; rare)	E
Nervous System	Anxiety (10%)	E
	Confusion (or cognitive changes, < 1%)	E
	Depression (15%) (may be severe)	E
	Dizziness (19%)	E
	Headache (37%) (or migraine)	E
	Insomnia (15%)	E
	Paresthesia , optic neuritis (<10%)	E
Ophthalmic	Conjunctivitis (<10%)	E
Renal	Renal failure (<1%)	E
Respiratory	Cough, dyspnea (20%)	E
	Pneumonitis (rare)	D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for imatinib include fluid retention (including effusions), musculoskeletal pain, nausea, vomiting, diarrhea, rash, fatigue, abdominal pain, headache, infection, bleeding and abnormal electrolyte(s).

Superficial edema was a common finding in all studies described primarily as periorbital edema or lower limb edema. Edema is rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib. **Severe fluid retention** includes pleural effusion, pericardial effusion, pulmonary edema, ascites, or superficial edema and rapid weight gain. Interruption of imatinib treatment, diuretics and other supportive care measures usually managed these events. Edema and fluid retention are dose-related and are more common with higher doses.

Myelosuppression occurred frequently and incidence was more common at higher dosages, in blast crisis and accelerated phase than in the chronic phase of CML. Reducing the dosage or interrupting treatment will usually manage the cytopenic events, while hemoglobin usually returns to baseline values with continued therapy.

Reactivation of hepatitis B virus (HBV) has been reported in patients who are chronic carriers of HBV and received BCR-ABL TKI's. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV

infection prior to initiating treatment. Carriers of HBV must be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Subdural hematoma (up to 2%) has been reported with imatinib use with other risk factors, such as age > 50 years, thrombocytopenia (disease or medication-related), concurrent medications that increase bleeding risk, prior lumbar puncture or head trauma. Patients who experience head trauma or have unusual neurologic symptoms should be evaluated for subdural hematoma.

Gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal hemorrhage was reported in post-marketing after about one year of treatment (variable onset). Monitor patients for symptoms of GI hemorrhage throughout therapy and consider imatinib discontinuation, as appropriate.

Hepatotoxicity was reported with severe elevation of transaminases or bilirubin and may be fatal. Gastrointestinal or intratumour bleeds have been reported in patients with GIST, and concomitant use of warfarin or antiplatelet agents should be avoided.

Falls in LVEF and **cardiac** failure have been reported especially in patients with pre-existing risk factors such as hypertension, coronary artery disease and diabetes. Cardiogenic shock has been reported in patients with hypereosinophilia and cardiac involvement and may be reversible with steroids and supportive care.

GI obstruction and **perforation** has been reported in all tumour types.

Severe skin reactions have been observed including Stevens-Johnson syndrome, toxic epidermal necrolysis, leucocytoclastic vasculitis, Sweet's syndrome, erythema multiforme and DRESS (Drug reaction with eosinophilia and systemic symptoms) which may be life-threatening.

Patients at risk of **tumour lysis syndrome** should have appropriate prophylaxis and be monitored closely.

Long term treatment with imatinib may result in **declines in renal function**. In treatment-naïve patients with newly-diagnosed CML initiated on imatinib among three Phase III trials, a progressive decline in eGFR from a median baseline value of 100 ml/min/1.73m^2 to 85.5 ml/min/1.73m^2 at 5 years was observed. A study evaluating the incidence of acute kidney injury and chronic kidney disease (CKD) in chronic-phase CML patients treated with tyrosine kinase inhibitors found that imatinib treatment was associated with a CKD incidence of 22% (Yilmaz 2015).

Musculoskeletal pain may persist for months in 18-46% of CML patients following discontinuation of long-term treatment (imatinib withdrawal symptoms).

Osteonecrosis has been reported, including severe cases requiring treatment discontinuation, and /or surgical intervention. The most affected site was the femur head; other affected sites included the tibia, femur shaft, jaw, finger, and calcaneus.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients with hypereosinophilia (e.g. MDS, HES) should be started on 1-2mg/kg of prednisone at least 2 days before imatinib is started and continued for 1-2 weeks.

Dose levels are 200mg, 300mg, 400mg, 600mg, and 800mg.

800 mg dose should be given as 400 mg BID, to reduce iron exposure.

Adults:

Indication		Daily Starting Dose	Escalate?
CML	New diagnosis	400mg	Yes[1] → 600 or 800mg
	Chronic	400mg	Yes[1]→ 600 or 800mg
	Blast crisis/accelerated	600mg	Yes[1] → 800mg
ALL Ph+ (monotherapy)		600mg	No
MDS/MPD		400mg	No
Systemic mastocytosis – with eosinophilia		100mg	Yes[2] → 400mg
Systemic mastocytosis – no eosinophilia (mutation status unknown, cKIT negative or not responding to other treatment)		400mg	No
HES/CEL		100mg	Yes[2] → 400mg
DFSP		800mg	No
GIST (metastatic/unresectable)		400mg or 600mg	Yes[2] → 600mg or 800mg
GIST (adjuvant) (one year duration)		400mg	No

1. in absence of severe toxicity if progression (± prior response), no hematologic response after 3 months or no cytogenetic response after 12 months
2. In absence of toxicity if insufficient response to treatment.

Dosage with Toxicity:

Toxicity	Action
Fluid retention (grade 3,4)	Hold until ≤ grade 1; resume with 1 dose level ↓.
Rash (grade 3, 4)	Hold until ≤ grade 1; resume with 1 dose level ↓ or discontinue.
Bilirubin 3 x ULN OR AST or ALT > 5 x ULN	Hold*; resume with 1 dose level ↓.
Hypotension / Hypersensitivity reaction	Hold, treat supportively, consider steroids.
Bleeding	Hold; consider discontinuing if severe.
Pneumonitis	Hold, investigate, consider discontinuing if confirmed.
DRESS	Consider discontinuing.

*Hold until bilirubin < 1.5 x ULN, and AST or ALT < 2.5 x ULN.

Dosage with Myelosuppression:

Monotherapy:

	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
Accelerated, blast crisis CML or Ph+ ALL (600 mg starting dose)	< 0.5	< 10	• If related to disease (i.e., marrow), consider escalating dose. • If unrelated to leukemia ↓ one dose level. • If no recovery in 2 weeks, ↓ further by one dose level. • If no recovery in further 2 weeks, hold until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L and then resume treatment without further dose reduction.
All others:			
Starting dose 100mg	< 1	< 50	• Hold until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. • Then resume treatment at previous dose.
Starting dose 400-600mg	< 1	< 50	• Hold until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L and then resume treatment at previous dose. • If recurs, hold until recovery and restart with one dose level ↓.

Starting dose 800mg	< 1	< 50	• Hold until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L and then resume treatment with one dose level ↓. • If recurs, hold until recovery; resume by further ↓ one dose level.

Dosage with Hepatic Impairment:

Imatinib is excreted via the liver and increased exposure is likely in the presence of hepatic impairment.

Starting Dose (for usual starting dose range of 400-800 mg daily):

Hepatic Impairment	Recommended Imatinib Starting Dose
Mild (bilirubin ≤ 1.5 x ULN with AST or ALT > ULN)	400 mg daily
Moderate (bilirubin > 1.5 to 3 x ULN)	400 mg daily
Severe (bilirubin > 3 X ULN)	200 mg daily; may consider ↑ to 300 mg daily if no severe toxicity

Toxicity During Treatment: Refer to Dosage with Toxicity section.

Dosage with Renal Impairment:

Imatinib is not excreted via the kidney to a significant extent; however, increased exposure and adverse effects are correlated with renal impairment. Exercise caution in patients with mild to moderate renal impairment.

Starting Dose (For usual starting dose range 400-800 mg daily):

Creatinine Clearance (mL/min)	Recommended Imatinib Starting Dose
40-59	400 mg daily.* Use with caution.
20-29	400 mg daily.*† Use with caution.
<20 or on hemodialysis	Not recommended for use

* May adjust dose based on toxicity, or for lack of efficacy if lower dose was tolerated.
† Doses ≥ 800 mg daily have not been studied.

Dosage in the elderly:

Efficacy was similar in patients ≥ 65 years of age compared to younger patients in CML and adjuvant GIST.

In adjuvant GIST, no difference in safety was observed in patients aged ≥ 65 years compared to younger patients.

Children:

There is no experience with imatinib in CML in pediatric patients under 2 years of age. Very limited to no experience exists for imatinib in children in other indications. Children have a higher incidence of electrolyte and glucose abnormalities than adults. Start at 340mg/m^2 (do not exceed 600mg). Reduce dose to 260mg/m^2 as needed – consult product monograph for details. Monitor growth closely in children and adolescents under imatinib treatment as there have been case reports of growth retardation.

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F - Administration Guidelines

- Tablets should be administered whole with meal(s) and a large glass of water to reduce gastric irritation.
- Doses < 800mg should be given once daily; total daily doses of 800mg should be given as 400mg twice daily to reduce exposure to iron.
- If unable to swallow the tablet:
  - The **400 mg** tablet may be broken into two pieces; administer each piece with water, one after the other.
  - Alternatively, tablet may be dispersed in water or apple juice (use 50 mL for 100 mg tablet, and 200 mL for a 400 mg tablet) immediately before drinking this mixture. Then, rinse the container with water or apple juice and drink this, to ensure no trace of the tablet is left.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, the patient should skip this dose and take the next dose at the usual time.
- If vomiting occurs after taking a dose, do not take an extra dose. Take the next dose at the usual time.
- Store at room temperature.

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to imatinib or to any other components of this product

Other Warnings/Precautions:

- Severe fluid retention may occur, especially with higher doses. Patients should be weighed and monitored regularly. Patients with pre-existing cardiac disease, risk factors for cardiac failure or the elderly should be monitored carefully and be treated appropriately.
- Severe bleeding, including GI, CNS and intra-tumoural, have been reported during clinical trials and post-marketing. Use caution with the concomitant use of imatinib and other drugs that may increase bleeding (e.g. anticoagulants, antiplatelets or prostacyclins). Consider the use of LMWH rather than warfarin if anticoagulation is required.

Other Drug Properties:

- Carcinogenicity:
  Neoplastic changes were observed in animal studies. Relevance of these findings for humans is unknown. In clinical trials, the numbers of cancers reported were similar to those expected in the general population.

Pregnancy and Lactation:

- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Teratogenicity: Documented in humans
- Abortifacient effects: Documented in humans
- Pregnancy:
  Imatinib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **15 days** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Excretion into breast milk: Yes
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **15 days** after the last dose.
- Fertility effects: Yes
  Fertility may be affected in patients who produce sperm.

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H - Interactions

Imatinib is mainly metabolized by CYP3A4. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play minor roles in metabolism of imatinib.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ Imatinib exposure (40% with ketoconazole)	↓ metabolism	Caution
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc.)	↓ Imatinib exposure (74% with rifampin)	↑ metabolism	Caution; consider using drugs with less enzyme induction potential

CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ plasma concentration of CYP3A4 substrate	Imatinib inhibits CYP 3A4	Caution; especially drugs with narrow therapeutic index
CYP2D6 substrates (e.g. cyclophosphamide, beta blockers, morphine, oxycodone, metoprolol, serotonin-H3 antagonists)	↑ plasma concentration of CYP2D6 substrate (23% for metoprolol)	Imatinib inhibits CYP2D6	caution, especially drugs with narrow therapeutic index
CYP 2C9 substrates (e.g. warfarin)	↑ substrates' concentrations, or ↑ anticoagulant effect for warfarin (theoretical)	Imatinib inhibits CYP2C9 at high doses	Caution, monitor INR closely with warfarin, especially during imatinib initiation or dose adjustments, or consider LMWH for coagulation
Antiplatelet agents or other anticoagulants	↑ risk of bleeding	Additive	Avoid; if must co-administer, monitor INR and platelets closely
acetaminophen	Exacerbation of hepatotoxicity, increased acetaminophen exposure (fatal case reported)	inhibits o-glucuronidation	Caution; monitor LFTs

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline; weekly for first month, biweekly for second month, and as indicated thereafter (e.g. every 2 to 3 months)
Liver function tests	Baseline, monthly, or as clinically indicated
Electrolytes, serum creatinine and creatinine clearance	Baseline, monthly or as clinically indicated
INR for patients taking warfarin, especially when starting treatment and with imatinib dose adjustments	Baseline and as clinically indicated
TSH levels in patients with previous thyroidectomy or patients on replacement therapy	Baseline and as clinically indicated
LVEF, in patients with known underlying heart disease or in elderly patients	Baseline and as clinically indicated
Close monitoring of growth in younger patients	Baseline and as clinically indicated
Platelet counts and prothrombin time when imatinib is used concurrently with anticoagulants, prostacyclins, or other medications that increase bleeding risk	Baseline and periodic
Clinical assessment of fluid retention (including weight monitoring), bleeding, infection, cardiac effects, thromboembolism, rhabdomyolysis, tumour lysis syndrome, osteonecrosis, gastrointestinal effects, pneumonitis, and rash	At each visit
Brain imaging for patients suspected of having subdural hemorrhage	As clinically indicated
Serum or urine pregnancy test in women of childbearing potential	Within one week before starting treatment

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
EKG and troponin in patients with hypereosinophilia and cardiac involvement	As clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- iMAtinib - Refer to listed Health Canada indications for generic imatinib formulations. Patients must meet generic substitution policies for access to Gleevec®

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K - References

BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC (imatinib mesylate), TASIGNA (nilotinib), BOSULIF (bosutinib), SPRYCEL (dasatinib), ICLUSIG (ponatinib hydrochloride)] - Risk of Hepatitis B Reactivation. Health Canada, May 4, 2016. [Accessed May 13, 2016]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/58222a-eng.php

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December 2024 Modified Dosage with myelosuppression section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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