Drug Monograph

A - Drug Name

iMAtinib

COMMON TRADE NAME(S): Gleevec®

back to top

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	Oral: Yes (bioavailability 98%). 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	N-demethylated piperazine derivative
	Inactive metabolites	yes
Elimination	Imatinib is eliminated predominantly by fecal excretion (68%) and in urine (13%) within 7 days.	
	Half-life	18 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Adult patients with newly diagnosed, Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in chronic phase
- Pediatric patients with newly diagnosed Ph+ CML in chronic phase
- Adult patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- As a single agent for induction phase therapy in adult patients with newly diagnosed, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL).
- As monotherapy in the treatment of adult patients with relapsed or refractory Ph+ALL
- Treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD) either without the D816V c-Kit mutation, or unknown.
- Adult patients with unresectable recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement
- Unresectable and/or metastatic Kit (CD117) positive gastrointestinal stromal tumours (GIST) in adults
- Adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST

Note:

Approvals are based on surrogate endpoints (such as response based endpoints). Overall survival data are not available.

back to top

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 (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
	Tumor lysis syndrome (rare)	I E
Musculoskeletal	Avascular necrosis (rare)	E
	Musculoskeletal pain (50%) (includes withdrawal syndrome)	E
	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).

back to top

E - Dosing

Patients with hypereosinophilia (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?	Hepatic Impairment		Renal Impairment (Clcr; mL/min)	
				Mild-mod[6]	Severe[7]	20-59	<20
CML	New diagnosis	400mg	Yes[1] → 600 or 800mg	3	4, 5	3	Discontinue
	Chronic	400mg	Yes[1]→ 600 or 800mg	3	4, 5	3	Discontinue
	Blast crisis/accelerated	600mg	Yes[1] → 800mg	3	4, 5	3	Discontinue
ALL PH+		600mg	No	3	4, 5	3	Discontinue
MDS/MPD		400mg	No	3	4, 5	3	Discontinue
Systemic mastocytosis – with eosinophilia		100mg	Yes[2] → 400mg		4, 5	3	Discontinue
Systemic mastocytosis – no eosinophilia (mutation status unknown, cKIT negative or not responding to other treatment)		400mg	No	3	4, 5	3	Discontinue
HES/CEL		100mg	Yes[2] → 400mg		4, 5	3	Discontinue
DFSP		800mg	No	3	4, 5	3	Discontinue
GIST (metastatic/unresectable)		400mg or 600mg	Yes[2] → 600mg or 800mg	3	4, 5	3	Discontinue

GIST (adjuvant) (one year duration)	400mg	No	3	4, 5	3	Discontinue

1. in absence of severe toxicity if progression (± prior response), no hematologic response after 3 months or cytogenetic response after 12 months
2. In absence of toxicity if insufficient response to treatment.
3. Start at 400 mg. For mild renal impairment only (Clcr = 40-59 mL/min), may consider escalation (if applicable in table) if inadequate efficacy providing lower dose well-tolerated.
4. Initially, start at 200 mg. If no toxicity may ↑ to 300mg.
5. While on treatment: Hold until bilirubin < 1.5 x ULN and AST/ALT < 2.5 x ULN and then restart by ↓ 1 dose level
6. bilirubin > 1.5 - 3 x ULN or AST/ALT > ULN with bilirubin ≤ 1.5 x ULN
7. bilirubin > 3 x ULN or AST/ALT > 5 x ULN

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
Hypotension / Hypersensitivity reaction	Hold, treat supportively, consider steroids
Bleeding	Hold; consider discontinuing if severe
Pneumonitis	Hold, investigate, consider discontinuing if confirmed
DRESS	Consider discontinuing

Dosage with myelosuppression:

	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
Accelerated, blast crisis CML or Ph+ ALL	< 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. See dosage table.

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. See dosage table.

Dosage in the elderly:

There is no evidence of an increase in toxicity in patients older than 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.

back to top

F - Administration Guidelines

- Should be administered orally 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 a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.
- If unable to swallow, 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.

back to top

G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Consultation with a liver disease expert is recommended prior to starting imatinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment

- Imatinib results in serious fluid retention in 6% of patients, 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.
- Bleeding, including GI, CNS and intra-tumoural, have been reported in patients with GIST; concomitant use of warfarin or antiplatelet agents should be avoided. Consider the use of LMWH rather than warfarin if anticoagulation is mandatory.
- Exercise caution if drugs that may increase bleeding (e.g. anticoagulants, antiplatelets or prostacyclins) must be used.

Other Drug Properties:

- Carcinogenicity: Imatinib is potentially carcinogenic.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Imatinib is **contraindicated during pregnancy**. Spontaneous abortions have been reported in women who have taken imatinib. Highly effective contraception (failure rate < 1%) is recommended for both sexes during treatment, and for at least 6 months (general recommendation) after imatinib cessation.
  Women of childbearing potential should have a negative serum or urine pregnancy test (with a sensitivity of at least 25 mIU/ml) within one week before starting therapy.
- Breastfeeding:
  Breastfeeding is not recommended. Imatinib and/or its metabolites are excreted in human milk.
- Fertility effects: Probable
  Fertility may be affected in males.

back to top

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	↑ Imatinib exposure (40% with ketoconazole)	↓ metabolism	Caution

starfruit)			
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ Imatinib exposure (74% with rifampin)	↑ metabolism	Caution
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 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

back to top

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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
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
Electrolytes, serum creatinine and creatinine clearance	Baseline, monthly or as clinically indicated
Liver function tests	Baseline, monthly, or as clinically indicated
CBC	Weekly for first month, biweekly for second month, and as indicated thereafter (e.g. every 2 to 3 months)
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 and gastrointestinal effects, pneumonitis, 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
HBV infection status	Prior to starting treatment (or if on treatment and not previously tested or suspect infection); consult

	infectious disease if positive
For carriers of HBV: signs and symptoms of active HBV infection	At each visit during treatment and for several months after treatment discontinues

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

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- iMAtinib - Metastatic Gastrointestinal Stromal Tumours, with specific criteria
- iMAtinib - Adults with newly diagnosed Ph+ ALL, with specific criteria
- iMAtinib - Adjuvant Gastrointestinal Stromal Tumours, with specific criteria

ODB - General Benefit (with Therapeutic Notes) (ODB Formulary)

- iMAtinib - For treatment of Ph+ CML in chronic phase, blast phase or accelerated phase, with specific criteria

back to top

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

Druker BJ, Sawyers CL. Kantarjian H, et al. Activity of a specific inhibitor or the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. NEJM 2001;344(14):1038-42.

Gibbons J, Egorin MJ, Ramanathan RK, et al. Phase I and pharmacokinetic study of imatinib

mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol; 2008; 26:570-576.

Lyseng-Williamson K, Jarvis B. Imatinib. Drugs 2001: 61(12): 1765-1776.

Product Monograph: Gleevec. Novartis Pharmaceuticals Canada. November 24, 2017.

Ramanathan RK, Egorin MJ, Takimoto CHM, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol; 2008; 26:563-569.

Savage DG, Antman KH. Imatinib Mesylate – a new oral targeted therapy. NEJM 2002; 346(9): 683-93,

Yilmaz M, Lahoti A, O'Brien S, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer; 2015; 121(21): 3894-904.

June 2019 Updated emetic risk category.

back to top

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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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back to top