Drug Monograph

A - Drug Name

daSATinib

COMMON TRADE NAME(S): Sprycel®

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B - Mechanism of Action and Pharmacokinetics

Dasatinib inhibits multiple tyrosine kinases including BCR-ABL (including mutations other than T315I), SRC family, c-KIT, ephrin (EPH) receptor, and platelet-derived growth factor receptor (PDGFR-β). Kinase inhibition halts proliferation of leukemia cells. Dasatinib has activity in preclinical models against imatinib resistant models.

Absorption	Pharmacokinetics are linear with increasing dosage.	
	Bioavailability	Rapidly absorbed following oral administration. The adjusted geometric mean ratio was 0.84 for AUC in healthy adults who received tablets dispersed in juice (compared with intact tablets).
	Peak plasma levels	0.25-6 hours
	Effects with food	Food did not result in a clinically significant change in exposure.
Distribution	Dasatinib is extensively distributed throughout the body with a large volume of distribution.	
	PPB	Yes (96% to parent drug and 93% to active metabolite)

Metabolism	Dasatinib is extensively metabolized primarily by CYP3A4. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of metabolites.	
	Active metabolites	Yes, minor role in overall pharmacologic activity.
	Inactive metabolites	Yes
Elimination	Half-life	3-5 hours (terminal)
	Urine	4%; 0.1 % as unchanged drug
	Feces	85%; 19% as unchanged drug

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C - Indications and Status

Health Canada Approvals:

- Acute Lymphoblastic Leukemia (ALL)
- Chronic myeloid leukemia (CML)

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

Extravasation Potential: Not applicable

The following table contains adverse effects reported for imatinib resistant or intolerant chronic phase CML treatment using 100 mg per day in phase 3 studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Other - Hearing loss including tinnitus, vertigo (< 5%)	E
Cardiovascular	Arrhythmia (8%) (palpitations, tachycardia; atrial/ventricular arrhythmia - rare)	E
	Arterial thromboembolism (<1%)	E
	Cardiotoxicity (4%)	E D
	Hypertension (9%)	E
	Myocarditis (<1%)	E
	Pericardial effusion (1%) (severe)	E
	Pericarditis (<1%)	E
	Pulmonary hypertension (5%)	E D L
	QT interval prolonged (<1%)	E
	Venous thromboembolism (<5%)	E
Dermatological	Alopecia (8%)	E
	Dry skin (6%)	E
	Erythema multiforme (rare)	E
	Hyperhidrosis (10%)	E
	Photosensitivity (<5%)	E
	Rash, pruritus (33%)	I E
	Stevens-Johnson syndrome (rare)	E
Gastrointestinal	Abdominal pain (24%)	E
	Anorexia (7%)	E
	Constipation (18%)	E
	Diarrhea (42%) (4% severe)	I E
	Dyspepsia (8%) (or gastritis)	E
	GI ulcer (<1%)	E
	Mucositis (10%)	E
	Nausea, vomiting (22%)	I E
	Weight changes (11%)	E D
General	Fatigue (37%)	E
	Fluid retention (28%) (pleural and pericardial effusions, 5% severe)	E D L
Hematological	Hemorrhage (27%) (including GI, CNS; 3% severe)	E D
	Myelosuppression (36%) (severe)	E
	Other (<1%) (Coagulopathy)	E

	Pure red cell aplasia (<1%)	E
	Thrombotic microangiopathy (rare)	E
Hepatobiliary	Cholecystitis (<1%)	E
	↑ LFTs (<1%) (severe)	E
	Pancreatitis (<1%)	E
Hypersensitivity	Hypersensitivity (5%) (1% severe)	I
Infection	Infection (48%) (severe, including atypical infections, viral re-activation)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (10%) (↓ Ca, K, PO4 grade 3-4)	E
	Hyperuricemia (5%)	E
	Tumour lysis syndrome (<1%)	I E
Musculoskeletal	Musculoskeletal pain (48%) (including spasms)	E
	Rhabdomyolysis (<1%)	E
Nervous System	Anxiety (5%)	E
	Confusion (<5%)	E
	Depression (11%)	E
	Dizziness (16%)	E
	Dysgeusia (<5%)	E
	Headache (48%)	I E
	Insomnia (12%)	E
	Neuropathy (14%)	E
	Seizure (<5%)	E
Ophthalmic	Conjunctivitis (<5%)	E
	Eye disorders (7%)	E
Renal	Proteinuria (<1%) (including nephrotic syndrome)	E
	Renal failure (6%) (observed with 140mg daily)	E
Reproductive and breast disorders	Gynecomastia (<5%)	E
	Irregular menstruation (<1%)	E
Respiratory	Cough, dyspnea (34%)	E
	Pneumonitis (<5%)	E

* "*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 dasatinib include headache, infection, musculoskeletal pain, diarrhea, fatigue, myelosuppression, cough/dyspnea, rash/pruritus, fluid retention and hemorrhage.

Severe myelosuppression is common, especially in patients with advanced CML and Ph+ ALL. Severe febrile neutropenia (including fatal outcomes) was reported. Myelosuppression was generally reversible after a short hold with or without dose reduction.

Dasatinib may cause severe or fatal **bleeding** (including CNS); the most frequent hemorrhage site was gastrointestinal. Fatal bleeds have been reported more than 30 days after treatment discontinuation. Most bleeding events in clinical studies were associated with severe thrombocytopenia, although dasatinib may also cause platelet dysfunction.

Fluid retention is common (up to 47% after 5 years), may be severe, and can result in pleural and pericardial effusions, pulmonary edema, congestive heart failure, and ascites. Paracentesis may be required. Fluid retention may be managed by supportive care measures that include diuretics or short courses of steroids.

Pulmonary hypertension has been described and may present after more than 1 year of treatment with non-specific symptoms such as fatigue and dyspnea. If suspected, treatment with dasatinib should be held during investigation.

Reactivation of hepatitis B virus (HBV) has been reported in patients who received BCR-ABL TKI's and are chronic carriers of HBV. 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.

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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.

Hypokalemia and hypomagnesemia should be corrected before starting dasatinib.

Patients should be tested for HBV infection prior to initiating treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating treatment.

Adults:

Indication	Starting Dose (mg; PO once daily)	Escalation (if hematologic or cytogenetic response not achieved) (mg; PO once daily)
Chronic phase CML	100	May escalate to 140
All other	140	May escalate to 180

Dosage with Toxicity:

Dose Level	Dasatinib Dose (mg; PO once daily)	
	Chronic phase CML	Accelerated, blast phase CML; Ph+ALL
0	100	140
-1	80	100
-2	50	80

Dosage with Myelosuppression:

Indication	Blood Counts (x 10^9/L)	Action (Blood Counts x 10^9/L)
Chronic phase CML	ANC <0.5 and/or Platelets <50	1. Hold until ANC ≥ 1 and platelets ≥ 50 2. Resume at same dose level 3. If platelets < 25 and/or recurrence of ANC < 0.5 for > 7 days, repeat step 1 and resume at ↓ 1 dose level for second episode 4. Third episode: further ↓ by 1 dose level (newly diagnosed patients) or discontinue (patients resistant or intolerant to prior therapy including imatinib) 5. Fourth episode: Discontinue

Accelerated or blast phase CML; Ph+ALL	ANC <0.5 and/or Platelets <10	If related to leukemia (bone marrow biopsy), consider ↑ to 180 mg OD. If unrelated: 1. Hold until ANC ≥1 and platelets ≥20 2. Resume at same dose level 3. Second episode: repeat step 1 and resume at ↓ 1 dose level 4. Third episode: repeat step 1 and resume by further ↓ 1 dose level 5. Fourth episode: Discontinue

Dosage with non-hematologic toxicity:

Toxicity	Grade	Action
Fluid retention	Any	Hold if appropriate until recovery and treat with diuretics, short courses of steroids or other supportive measures. Consider dose reduction or treatment discontinuation.
Pulmonary hypertension	Any	Hold and investigate. Discontinue if confirmed.
Mucocutaneous skin reactions	Severe or any grade SJS	Discontinue (if no other etiology).
Other non-hematologic toxicity	Grade 2	Hold until recovery. First occurrence: resume at same dose level. Second occurrence: resume at ↓ 1 dose level.
	≥ Grade 3	Hold until recovery. Restart at a reduced dose if appropriate.

Dose Reduction for concomitant use of strong CYP3A4 inhibitors:

Current Dasatinib Dose (mg/daily)	Reduced Dasatinib Dose (mg/daily)*
140	40
100	20
70	20
60	Hold until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before restarting dasatinib.
40	

*If dasatinib is not tolerated after dose reduction, discontinue the strong CYP3A4 inhibitor or hold dasatinib until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before dasatinib dose is increased.

Dosage with Hepatic Impairment:

Dasatinib has not been studied in hepatic impairment within the indicated dosing range. Hepatic metabolism / excretion is significant; caution should be exercised and dose modification considered especially for moderate or severe hepatic impairment.

Dosage with Renal Impairment:

Studies in renal impairment have not been conducted. However, since <4% of dasatinib and metabolites are renally excreted and a reduction in dasatinib clearance is not expected.

Dosage in the elderly:

No dose adjustment is required. Patients ≥ 65 years of age are more likely to experience commonly reported adverse events, such as diarrhea, fatigue, cough, dyspnea, fluid retention (including pericardial and pleural effusion), dizziness, pneumonia, hypertension, arrhythmia, heart failure, and gastrointestinal bleeding, as well as less frequently reported events such as pulmonary edema, lung infiltration, arthritis and urinary frequency. Imatinib resistant or intolerant chronic phase CML patients are less likely to have major cytogenetic response. Monitor closely.

Children:

Not recommended for use in children < 18 years, since safety and effectiveness have not been established in these patients. Do not use in children < 2 years of age as increased toxicity and mortality have been observed in young animals.

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F - Administration Guidelines

- Swallow tablet whole with or without food once daily.
- Tablets should not be crushed or cut.
- Antacids should be avoided; if required, they should be taken up to 2 hours before or 2 hours after the administration of dasatinib.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, skip this and give the next dose as scheduled. Do not double the dose to make up for the forgotten one.
- Pregnant women should avoid exposure to crushed and/or broken tablets.
- Store at room temperature (15°C to 30°C).

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to dasatinib or its components
- Breastfeeding women

Other Warnings/Precautions:

- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Consultation with a liver disease expert is recommended prior to starting dasatinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment.
- Dasatinib and its metabolite may prolong the QT interval, and should be used with caution in patients at risk, such as those with hypokalemia, hypomagnesemia, congenital long QT syndrome, on antiarrhythmic therapy or other medications that may lead to QT prolongation, or in patients who have received cumulative high-dose anthracyclines.
- Use with caution in patients with uncontrolled or significant cardiovascular disease as they were excluded from clinical trials. Adverse cardiac events were more frequent in patients with cardiovascular risk factors or a previous medical history of cardiac disease.
- Exercise caution in patients at risk of bleeding or who are taking concurrent anticoagulants, as dasatinib has been shown to inhibit platelet aggregation and increase bleeding time. Patients with a history of significant bleeding disorder unrelated to CML were excluded from dasatinib clinical studies.
- Patients with pre-existing pleural effusion were excluded from phase III studies.
- Use with extreme caution when fluid loading/transfusing.

Other Drug Properties:

- Carcinogenicity: Documented in animals

Pregnancy and Lactation:

- Clastogenicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
- Pregnancy:
    - Dasatinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment and for at least **6 months** after the last dose (general recommendation).
    - Spontaneous abortion and fetal/infant anomalies have been reported post-marketing.
- Breastfeeding: Contraindicated
- Fertility effects: Probable
  Documented in animal studies in female animals

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H - Interactions

Dasatinib is primarily metabolized by CYP3A4 and is susceptible to interactions with inhibitors and inducers of this isoenzyme. Dasatinib is not an inducer of CYP enzymes, and does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1, but does inhibit CYP3A4.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ dasatinib exposure (up to 5-fold with ketoconazole)	↓ dasatinib metabolism	Avoid concomitant usage with strong inhibitors; consider dasatinib dose reduction if a strong CYP3A4 cannot be discontinued. See Dosage with Toxicity for dasatinib dose reductions.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ dasatinib exposure and concentration (~80% with rifampin); QT ↑ observed when dasatinib and rifampin were taken 12h apart	↑ dasatinib metabolism	Avoid concomitant usage with strong inducers; consider alternative agents with less enzyme induction potential.
CYP3A4 substrates with narrow therapeutic index (i.e. macrolide antibiotics, benzodiazepine, pimozide, quinidine, ergot alkaloids, cyclosporine)	↑ substrates' concentrations (20% ↑ observed with simvastatin)	Dasatinib inhibits CYP3A4	Caution. The effect of a CYP3A4 substrate on the pharmacokinetic parameters of dasatinib has not been studied.
Drugs that prolong QT interval (simvastatin - CYP3A4 substrate as well)	additive effects	QT interval prolongation	Avoid concomitant usage if possible.
H2 blockers/ proton pump inhibitors (i.e. famotidine, omeprazole)	↓ dasatinib exposure and concentration (~60% with famotidine)	Suppression of gastric acid decreases bioavailability of dasatinib	Avoid concomitant usage; consider the use of antacid instead (e.g. aluminum hydroxide/magnesium hydroxide) ≥ 2hrs

			before or after dasatinib
Antacids (i.e. aluminum hydroxide/magnesium hydroxide)	↓ dasatinib exposure and concentration (~ 55%)	Suppression of gastric acid decreases bioavailability of dasatinib	Administer up to 2h before or 2h after the administration of dasatinib
Drugs that affect coagulation or inhibit platelet function	↑ bleeding risk	Additive with dasatinib's effect on ↑ platelet aggregation time	Caution; anticoagulants, NSAIDs, aspirin used in clinical trials if platelets > 50 x 10^9/L

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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	Chronic phase CML: baseline and every 2 weeks for 12 weeks, then every 3 months or as clinically indicated. Advanced phase CML or Ph+ALL: baseline and weekly for the first 8 weeks, then monthly or as clinically indicated
Liver and renal function tests (including electrolytes), creatine kinase	Baseline and every 2 weeks for the first 2 months, then monthly and as clinically indicated
LVEF evaluation, in patient with cardiac risk factors	Baseline and as clinically indicated
ECG	Baseline and as clinically indicated
Signs and symptoms of active HBV infection (in HBV carriers)	During treatment and for several months after treatment discontinuation
Clinical toxicity assessment for signs and symptoms of bleeding, infection, cardiotoxicity, muscle pain, rash, GI, pulmonary hypertension, pleural effusion, dermatological and auditory effects and fluid retention	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Consider LVEF evaluation in patients without cardiac risk factors.	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- daSAtinib - PH+ ALL, with specific criteria
- daSAtinib - Ph+ CML in the chronic phase, with specific criteria
- daSAtinib - Accelerated phase or blast phase Ph+ CML with documented resistance or intolerance to imatinib, with specific criteria

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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

Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2260-70.

Product Monograph: Sprycel®. Bristol-Myers Squibb Canada. August 25, 2020.

Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. Blood 2008; 26(19); 3204-12.

US Prescribing Information: Sprycel®. Bristol-Myers Squibb Company. March 2021.

February 2025 Updated Pregnancy and Lactation 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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