

**DRUG NAME: Dasatinib****SYNONYM(S):** BMS 354825<sup>1</sup>**COMMON TRADE NAME(S):** SPRYCEL®**CLASSIFICATION:** tyrosine kinase inhibitor*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Dasatinib inhibits multiple tyrosine kinases including BCR-ABL, the fusion protein created by the abnormal Philadelphia chromosome (Ph) which characterizes chronic myeloid leukemia.<sup>2,3</sup> Competitive inhibition at the enzyme's ATP-binding site leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction.<sup>2,3</sup> Inhibition is not completely selective, as dasatinib also inhibits other kinases including the Src family (LYN, HCK), c-kit, ephrin receptor (EPH), and platelet-derived growth factor receptor (PDGFR).<sup>2,3</sup> Dasatinib is structurally unrelated to imatinib and is approximately 300-fold more potent in terms of BCR-ABL inhibition.<sup>3,4</sup> Dasatinib may overcome imatinib resistance that results from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the Src family kinases, and multi-drug resistance gene overexpression.<sup>3</sup>

**PHARMACOKINETICS:**

Oral Absorption	rapidly absorbed; pH-dependent solubility; peak concentration: 0.5-3 h; food does not significantly affect systemic availability	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	2505 L; suggests distribution into extravascular space
	plasma protein binding <sup>5</sup>	96%; metabolite: 93%
Metabolism	extensive hepatic metabolism; involves the hepatic microsomal enzyme oxidation system (primarily CYP 3A4; flavin-containing mono-oxygenase-3 and uridine diphosphate-glucuronosyltransferase also involved <sup>5,6</sup> )	
	active metabolite <sup>3,5</sup>	N-dealkylated metabolite BMS 582691; minor role in pharmacology of dasatinib
	inactive metabolite(s) <sup>3,5</sup>	yes
Excretion	urine <sup>2,3</sup>	<4%; 0.1% as dasatinib
	feces <sup>2,3</sup>	85%; 19% as dasatinib
	terminal half life	5-6 h
	clearance	no information found
Sex	no clinically significant differences	
Elderly	no clinically significant differences	
Ethnicity	no clinically significant differences	

Adapted from standard reference<sup>2</sup> unless specified otherwise.**USES:****Primary uses:**

\*Leukemia, acute lymphoblastic (Ph+)

\*Leukemia, chronic myelogenous

\*Health Canada approved indication

**Other uses:**

**SPECIAL PRECAUTIONS:**

**Prolongation of the QT interval** may occur; use caution in patients with the following risk factors<sup>2</sup>:

- prolongation of QTc
- hypokalemia or hypomagnesemia
- thiamine deficiency<sup>7</sup>
- congenital long QT syndrome
- patients taking anti-arrhythmic medications or other medications that cause QT prolongation
- cumulative high-dose anthracycline therapy

**Caution:**

- with co-administration of a drugs that potentially alter **CYP 3A4** activity, prolong the QT interval, or are CYP 3A4 substrates of narrow therapeutic index<sup>2</sup>
- in patients who are at increased risk for **bleeding**, including those receiving anticoagulant medications<sup>2</sup>
- in moderate to severe **hepatic impairment**; clinical trials excluded patients with ALT and/or AST >2.5 times the upper limit of normal (ULN) and total bilirubin >2 times the ULN<sup>2</sup>
- dasatinib contains **lactose** and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption<sup>2</sup>
- **fluid retention** may occur<sup>2</sup>
- evaluate patients for signs and symptoms of **cardiopulmonary disease** prior to treatment as serious cases of pulmonary artery hypertension have been associated with dasatinib<sup>8</sup>
- **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<sup>9</sup>

**Carcinogenicity:** studies have not been performed to date<sup>2</sup>

**Mutagenicity:** Not mutagenic in Ames test. Dasatinib is clastogenic in mammalian *in vitro* mutation test. Dasatinib is not genotoxic in mammalian *in vivo* chromosome tests.<sup>2</sup>

**Fertility:** effect on male and female fertility not known<sup>2</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>3</sup> There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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).

Spontaneous abortion and fetal and infant anomalies have been reported by women taking dasatinib during pregnancy. Effective contraception is recommended during treatment with dasatinib.<sup>10,11</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>2</sup>

**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.<sup>12</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
allergy/immunology	<b>hypersensitivity (1-5%)</b>
auditory/hearing	<b>tinnitus (1-5%)</b>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
blood/bone marrow/ febrile neutropenia	<b>myelosuppression</b> (severe); typically reversible; severe thrombocytopenia and neutropenia considerably higher with dasatinib than with imatinib <sup>13</sup> ; pancytopenia <1%; see paragraph following <b>Side Effects</b> table
	<b>anemia</b> (severe 18-70%) <sup>5</sup>
	<b>neutropenia</b> (severe 49-83%) <sup>5</sup> ; febrile neutropenia (11%, severe 10%)
	<b>thrombocytopenia</b> (severe 48-83%) <sup>5</sup>
cardiovascular (arrhythmia)	arrhythmia (11%, severe 1%); palpitations (1-5%)
	change in QTc interval; see <b>Caution</b> section
cardiovascular (general)	cardiac dysfunction; cardiomegaly (1-5%); myocardial infarction (1-5%)
	<b>CHF/cardiac dysfunction</b> (5%, severe 3%); often triggered by an acute volume overload, including transfusions
	hypertension (1-5%)
	hypotension (5%, severe 1%)
	<b>pericardial effusion</b> (4%, severe 1%); see paragraph following <b>Side Effects</b> table
constitutional symptoms	chills (11%, severe <1%)
	fatigue (35%, severe 3%); asthenia (22%, severe 4%)
	fever (40%, severe 7%)
	hyperhidrosis (7%, severe 0%)
	insomnia (7%, severe 0%)
	weight gain (11%, severe <1%)
	weight loss (14%, severe 1%)
dermatology/skin	acne (1-5%)
	alopecia (7%, severe 0%)
	bruising (5%, severe 0%)
	flushing (7%, severe 0%)
	photosensitivity (<1%)
	pruritis (10%, severe 0%); dermatitis (1-5%); dry skin (1-5%) urticaria (1-5%)
	<b>rash</b> (34%, severe 1%); including erythematous, follicular, generalized, maculopapular, papular, pruritic, drug eruption, erythema multiforme, vesicular, and urticaria vesiculosa; manage with topical or systemic steroids, dose reduction, interruption, or discontinuation <sup>14</sup>
gastrointestinal	<i>emetogenic potential: low</i> <sup>15</sup>
	abdominal distention (10%, severe 0%)
	anorexia (17%, severe 1%); appetite disturbances (1-5%); dysgeusia (1-5%)
	ascites (severe 1%); see paragraph following <b>Side Effects</b> table
	constipation (13%, severe <1%)
	<b>diarrhea</b> (48%, severe 5%); rule out sources of infection, treatment may include standard supportive care and antidiarrheal treatment <sup>16</sup> ; see paragraph following <b>Side Effects</b> table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
	dyspepsia (7%, severe <1%)
	mucosal inflammation (15%, severe 1%); includes mucositis and stomatitis, <sup>17</sup> colitis and gastritis (1-5%)
	nausea (32%, severe 2%)
	vomiting (23%, severe 1%)
hemorrhage	<b>hemorrhage</b> (41%, severe 11%); including <b>gastrointestinal hemorrhage</b> (13%, severe 8%); CNS bleeding (2%, severe <1%); includes cerebral and intracranial hemorrhage and subdural hematoma; deaths have occurred; other hemorrhage (35%, severe 4%)
hepatobiliary/pancreas	cholecystitis (<1%), cholestasis (<1%), hepatitis (<1%)
infection	infection (29%, severe 7%); includes bacterial, viral, and fungal
	sepsis (6%, severe 5%); deaths have occurred
	upper respiratory tract infection (17%, severe 2%), pneumonia (12%, severe 8%); includes bacterial, viral, and fungal
lymphatics	<b>fluid retention</b> (49%, severe 9%); generalized edema (37%, severe 1%); peripheral edema; see paragraph following <b>Side Effects</b> table
metabolic/laboratory	elevated creatine phosphokinase (1-5%)
	elevated creatinine (severe 1-2%) <sup>6</sup>
	elevated liver function tests; more common with advanced disease; causality not established elevated alkaline phosphatase (severe 7%) <sup>6</sup>
	elevated ALT (severe 1-11%) <sup>6</sup>
	elevated AST (severe 1-8%) <sup>6</sup>
	elevated bilirubin (severe 1-5%) <sup>6</sup>
	elevated troponin (1-5%)
	hyperuricemia (1-5%)
	hypocalcemia (48-80%, severe 2-20%); calcium supplementation required (9-32%)
	hypophosphatemia (39-52%, severe 11-22%)
musculoskeletal	muscle inflammation, weakness, and stiffness (1-5%); rhabdomyolysis (<1%)
	panniculitis <sup>18</sup> ; case reports
neurology	anxiety (6%, severe <1%); depression (6%, severe 0%); confusional state (1-5%); affect lability (1-5%); somnolence (1-5%)
	convulsion (1-5%); tremor (1-5%)
	dizziness (12%, severe <1%); syncope (1-5%)
	neuropathy (12%, severe 1%); including peripheral neuropathy
ocular/visual	conjunctivitis (1-5%); dry eye (1-5%)
	periorbital edema (5-10%) <sup>6</sup>
pain	abdominal pain (25%, severe 2%)
	arthralgia (15%, severe 1%)
	chest pain (10%, severe 1%)
	headache (39%, severe 3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
	<b><i>musculoskeletal pain</i></b> (38%, severe 5%)
	myalgia (11%, severe 1%)
	pain not otherwise specified (21%, severe 2%)
pulmonary	cough (24%, severe 1%)
	<b><i>dyspnea</i></b> (31%, severe 7%); asthma (1-5%)
	<b><i>pleural effusion</i></b> (17%, severe 5%); decreased incidence with lower daily dosing <sup>4</sup> ; pulmonary edema (4%, severe <1%); see paragraph following <b>Side Effects</b> table
	pulmonary hypertension; see paragraph following <b>Side Effects</b> table
	<b><i>pulmonary infiltration</i></b> (1-5%); pneumonitis (1-5%)
renal/genitourinary	renal failure (1-5%)
	urinary frequency (1-5%)
syndromes	tumour lysis syndrome (1-5%)

Adapted from standard reference{{8909 Bristol-Myers Squibb Canada. 16 July 2007}} unless specified otherwise.

**The most frequently reported adverse effects** of dasatinib include fluid retention, gastrointestinal disturbances, fever, and bleeding.<sup>2,18</sup> Pleural effusions, peripheral edema, dyspnea/pulmonary edema, rash and headache may also occur.<sup>2,4,16</sup> The majority of non-hematologic toxicities are mild to moderate in severity.<sup>4,16</sup> Temporarily discontinue dasatinib if severe non-hematological adverse reactions occur until the condition improves or resolves.<sup>2</sup> The severity of the adverse reaction will determine when and at what reduced dose dasatinib should be restarted.<sup>2</sup>

**Fluid retention** including pleural and pericardial effusions, severe ascites, severe pulmonary edema, and generalized edema may occur.<sup>2</sup> Use caution in patients where fluid accumulation may be poorly tolerated, such as CHF, hypertension, and pulmonary disease.<sup>5</sup> **Severe pleural effusions** may be more prevalent (10%) in patients experiencing blast crisis.<sup>16</sup> Once-daily dosing is associated with fewer fluid-related adverse events<sup>19</sup> including pleural effusions.<sup>16</sup> Patients who exhibit signs and symptoms of pleural effusion, including dyspnea or dry cough should be evaluated by chest x-rays.<sup>16</sup> Recommendations for the management of pleural effusion<sup>16</sup>:

- temporary dasatinib discontinuation; the severity of the pleural effusion will dictate when and at what reduced dosage dasatinib treatment should be resumed
- diuretic therapy and short-term steroids<sup>2,3,14</sup>
- oxygen therapy, peritoneo-venous shunts, and thoracentesis may also be required for severe pleural effusion, but are generally not utilized clinically<sup>2</sup>

Serious cases of **pulmonary arterial hypertension (PAH)**, have been associated with dasatinib in post-marketing reports. Patients who develop symptoms such as dyspnea and fatigue after initiation of dasatinib should be evaluated for more common etiologies such as pleural effusion, pulmonary edema, anemia, or lung infiltration. Dasatinib should be withheld during evaluation if symptoms are severe, and permanently discontinued if PAH is confirmed.<sup>8</sup>

**Bone marrow suppression** is expected as BCR-ABL is responsible for abnormal hematopoiesis in CML patients.<sup>16</sup> Neutropenia, anemia, and thrombocytopenia are more common with advanced phase CML and Ph+ ALL,<sup>2</sup> likely due to increased Ph+ cell levels with CML disease progression.<sup>16</sup> Preliminary data in chronic phase CML suggests that 100 mg daily dosing is associated with a reduced incidence of myelosuppression, with comparable efficacy.<sup>14,16,19,20</sup> Management of myelosuppression includes:

- dose reduction, interruption, or rarely, discontinuation of dasatinib<sup>2</sup>
- blood and platelet transfusions<sup>2,4</sup>
- hematopoietic growth factors<sup>3,4,14,16</sup>

**Severe diarrhea** may be slightly more prevalent in dasatinib-treated accelerated phase (5%) and blast crisis (6%) patients.<sup>16</sup> Sources of infection should be ruled out and standard supportive care and antidiarrheal treatment provided.<sup>7,14,16</sup> If severe diarrhea occurs, discontinue dasatinib until the condition improves or resolves.<sup>2</sup> The severity of the diarrhea will dictate when and at what reduced dosage treatment can be resumed.<sup>2</sup>

**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.<sup>9</sup>

## INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit and grapefruit juice <sup>2</sup>	may increase pharmacological effect of dasatinib	may inhibit CYP 3A4 metabolism of dasatinib in the intestinal wall resulting in increased plasma levels of dasatinib	avoid grapefruit and grapefruit juice
H <sub>2</sub> blockers or proton pump inhibitors <sup>2,3,14</sup>	reduced pharmacological effect of dasatinib	pH-dependent solubility; reduced dasatinib plasma levels; reduced AUC (61%) and C <sub>max</sub> (63%) when famotidine administered concurrently	avoid concurrent use; consider switch to antacid; <b>See</b> aluminum hydroxide/magnesium hydroxide interaction below
aluminum hydroxide / magnesium hydroxide <sup>2</sup> and other antacids <sup>3,14</sup>	reduced pharmacological effect of dasatinib	pH-dependent solubility; reduced dasatinib plasma levels; reduced AUC (55%) and C <sub>max</sub> (58%) when administered concurrently	separate administration by 2 hours
simvastatin <sup>2</sup>	increased pharmacological and toxic effect of simvastatin including QTc prolongation	dasatinib may inhibit CYP 3A4 metabolism of simvastatin; increased simvastatin AUC (20%) and C <sub>max</sub> (37%)	consider alternate agents; use with caution

Dasatinib is a major CYP 3A4 substrate; therefore, drugs or herbs that are CYP 3A4 inducers may decrease the serum levels/effects of dasatinib. In addition, concomitant use of potent CYP 3A4 inducers is not recommended due to data demonstrating a risk of QTc prolongation.<sup>2</sup> If a CYP 3A4 inducer must be administered concomitantly, an increase in the dose of dasatinib should be considered with careful monitoring for toxicity.<sup>3,14,18</sup> St John's wort may cause unpredictable decreases in plasma dasatinib concentrations and should be avoided.<sup>3,14,21,22</sup>

Likewise, drugs or herbs that are CYP 3A4 inhibitors may increase the serum levels/effects of dasatinib.<sup>2,3,21</sup> If a strong CYP 3A4 inhibitor must be administered concomitantly, monitoring for toxicity and a decrease in the dasatinib dose should be considered.<sup>14,18</sup>

Dasatinib is a time-dependent weak inhibitor of CYP 3A4<sup>5,21</sup>; therefore, serum levels/effects of drugs or herbs that are CYP 3A4 substrates may be increased. Use caution, especially when administering dasatinib with a CYP 3A4 substrate of narrow therapeutic index.<sup>2,3,14,21</sup>

The effect of a CYP 3A4 substrate on the pharmacokinetic parameters of dasatinib has not been studied.<sup>2</sup>

## SUPPLY AND STORAGE:

**Oral:** Bristol Myers Squibb Canada supplies dasatinib as 20 mg, 50 mg, 70 mg, 80 mg, and 100 mg film-coated tablets. Selected non-medicinal ingredients: lactose.<sup>2</sup> Store at room temperature.<sup>2</sup>

**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 <b><i>bold, italics</i></b>
<i>Oral:</i>	<b><i>100-140 mg PO once daily</i></b> <sup>7,14,16,19,20</sup> <ul style="list-style-type: none"> <li>• may be taken without regard to food</li> <li>• separate administration of antacids by 2 hours</li> </ul>
	70 mg (range 50-100 mg) PO twice a day <sup>2,3</sup> <ul style="list-style-type: none"> <li>• may be taken without regard to food</li> <li>• separate administration of antacids by 2 hours</li> </ul>
<i>Concurrent radiation:</i>	close monitoring of blood counts required <sup>12</sup>
<i>Dosage in myelosuppression:</i>	<ul style="list-style-type: none"> <li>• for daily dosing refer to protocol by which patient is being treated<sup>7,14,16</sup></li> <li>• for twice daily dosing refer to product monograph<sup>2</sup></li> </ul>
<i>Dosage in renal failure:</i>	renal excretion of dasatinib and its metabolites is <4%; a decrease in total body clearance is not expected <sup>2</sup> ; no dosage details found
<i>Dosage in hepatic failure:</i>	primarily metabolized in the liver; use with caution with moderate to severe hepatic impairment <sup>2</sup> ; no dosage details found
<i>Dosage in dialysis:</i>	effect of dialysis on dasatinib pharmacokinetics has not been studied <sup>2</sup>

**Children:**

<i>Oral:</i>	safety and efficacy have not been established <sup>2</sup> ; currently being studied in children <sup>23,24</sup>
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