

## PRODUCT MONOGRAPH

<sup>Pr</sup>**SPRYCEL**\*

dasatinib

Tablets

20 mg, 50 mg, 70 mg and 100 mg dasatinib (as monohydrate)

Protein-tyrosine kinase inhibitor

Bristol-Myers Squibb Canada  
Montréal, Canada

\* TM of Bristol-Myers Squibb Company  
used under license by Bristol-Myers Squibb Canada

Date of Preparation:

22 March 2007

Date of Revision:

12 May 2010

Submission Control No: 135103

## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	9
DRUG INTERACTIONS .....	20
DOSAGE AND ADMINISTRATION.....	21
OVERDOSAGE .....	23
ACTION AND CLINICAL PHARMACOLOGY .....	24
STORAGE AND STABILITY.....	25
SPECIAL HANDLING INSTRUCTIONS .....	26
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	26
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>27</b>
PHARMACEUTICAL INFORMATION.....	27
CLINICAL TRIALS.....	27
DETAILED PHARMACOLOGY .....	37
TOXICOLOGY .....	38
REFERENCES .....	51
<b>PART III: CONSUMER INFORMATION.....</b>	<b>52</b>

# SPRYCEL

(dasatinib)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Non medicinal Ingredients
Oral	Tablet 20 mg, 50 mg, 70 mg and 100 mg	Lactose monohydrate. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

SPRYCEL (dasatinib) is indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) chronic, accelerated, or blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

Approval of SPRYCEL in CML is based on the rates of hematologic and cytogenetic responses in clinical trials with a minimum of 24 months of follow-up (see CLINICAL TRIALS).

SPRYCEL is also indicated for the treatment of adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy.

Approval in Ph+ ALL is based on the rates of hematologic and cytogenetic responses in clinical trials with a minimum of 24 months of follow-up (see CLINICAL TRIALS).

**Geriatrics (> 65 years of age):** While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention, congestive heart failure, gastrointestinal bleeding and dyspnea events and should be monitored closely. No differences in efficacy were observed between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and older (42% MCyR in patients  $\geq$  65 years versus 56% MCyR in the rest of the study population and 47% MCyR in patients  $\geq$  65 years versus 68% MCyR in the rest of the study population in studies CA180017 and CA180034, respectively).

**Pediatrics (< 18 years of age):** The safety and efficacy of SPRYCEL in patients <18 years of age have not been established (See WARNINGS AND PRECAUTIONS- Special populations).

## CONTRAINDICATIONS

Use of SPRYCEL is contraindicated in patients with hypersensitivity to dasatinib or to any other component of SPRYCEL.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- SPRYCEL (dasatinib) should only be prescribed by a qualified physician who is experienced in the use of antineoplastic therapy.
- Myelosuppression (thrombocytopenia, neutropenia, and anemia (see Warnings and Precautions – Myelosuppression)).
- Hemorrhage, including fatal outcomes (see Warnings and Precautions – Hemorrhage).
- Fluid retention, pleural effusion, pericardial effusion (see Warnings and Precautions – Fluid Retention).
- Congestive heart failure, pulmonary edema (see Warnings and Precautions – Fluid Retention and Cardiovascular).

### Myelosuppression

Treatment with SPRYCEL (dasatinib) is associated with thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding SPRYCEL temporarily or dose reduction (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS: Laboratory Abnormalities). Severe (CTC Grade 3 or 4) cases of anemia were managed with blood transfusions. Packed red blood cells were transfused in 30% of chronic phase CML patients and 79% of myeloid blast phase CML patients. Platelet transfusions were required in 17% of chronic phase CML patients and 66% of myeloid blast phase CML patients.

In a Phase III dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily (neutropenia 35%, thrombocytopenia 23% and anemia 13%) than in patients treated with 70 mg twice daily (neutropenia 45%, thrombocytopenia 38% and anemia 18%) (See ADVERSE REACTIONS).

## **Hemorrhage**

Patients were excluded from participation in initial SPRYCEL (dasatinib) clinical studies if they took medications that inhibit platelet function or anticoagulants. In subsequent trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with SPRYCEL if the platelet count was >50,000.

Overall, 198 (9.1%) patients experienced Grade 3-4 bleeding. Fifty (2%) patients experienced fatal bleeding.

Intracranial hemorrhage occurred in 48 (2.2%) of patients, of which 21 (0.96%) cases were considered related to SPRYCEL. Intracranial hemorrhage was fatal in 19 (0.9%) patients, of which nine (0.4%) cases were considered related to SPRYCEL.

Gastrointestinal hemorrhage regardless of relationship to SPRYCEL occurred in 13% of patients. The bleeding was severe in 6% of patients and generally required treatment interruptions and packed cell transfusions. Other episodes of severe bleeding occurred in 3% of patients

## **Fluid Retention**

SPRYCEL is associated with fluid retention, which was severe in 11% of patients, including severe pleural and pericardial effusion reported in 7% and 2% of patients, respectively (see ADVERSE REACTIONS). Severe ascites and generalized edema were each reported in <1% of patients. Other manifestations of fluid retention included pulmonary edema (3%), congestive heart failure/cardiac dysfunction (4%), and pericardial effusion (5%). Nineteen patients had severe pulmonary edema. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray.

Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. Pleural effusion required oxygen in some cases and at least one thoracentesis in 64 (3%) patients.

In the Phase III dose-optimization study in patients with chronic phase CML, Grade 3 or 4 fluid retention events were reported less frequently in patients treated with 100 mg once daily (5%) than in patients treated with 70 mg twice daily (11%) (See ADVERSE REACTIONS)

## **Cardiovascular**

Patients were excluded from enrolment of dasatinib trials for a broad range of cardiac events or conditions. A significantly abnormal ECG at screening was also an exclusion criterion. No prospective evaluation of cardiac function was carried out.

Congestive heart failure/cardiac dysfunction was reported in 96 (4%) of subjects during the study, of which 49 (2%) were considered to be severe. In some cases, the event was triggered by an acute volume load, including transfusion of blood products.

QT Prolongation: *In vitro* data suggest that dasatinib and its N-dealkylated metabolite, BMS-582691 have the potential to prolong cardiac ventricular repolarization (QT interval, see Safety Pharmacology). In 865 patients with leukemia treated with SPRYCEL in Phase II clinical studies, the mean changes from baseline in QTcF interval were 4–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <7 msec and lower 95% confidence interval for all mean changes from baseline were > -2 msec. Of the 2182 patients who received SPRYCEL in clinical studies, 21 patients (<1%) experienced a QTcF >500 msec.

SPRYCEL should be administered with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.

Hypokalemia or hypomagnesemia should be corrected prior to administration of SPRYCEL. (See Drug-Drug Interaction, ACTION AND CLINICAL PHARMACOLOGY: Electrocardiogram.)

### **Hepatic Impairment**

The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic impaired subjects who received a 50-mg dose and 5 severely hepatic-impaired subjects who received a 20-mg dose compared to matched healthy subjects who received a 70-mg dose of SPRYCEL. Hepatic impairment did not result in clinically meaningful change in dasatinib exposure at the doses studied. However no pharmacokinetic information is available from patients with hepatic impairment treated with a 70-100 mg dose of SPRYCEL (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics - Special Populations and Conditions). Due to the limitations of this clinical study, caution is recommended in patients with hepatic impairment.

In nonclinical studies, increased liver weight and foci of hepatocellular alteration were observed in rats, and hepatocellular vacuolation was observed in monkeys following repeat dose administration of dasatinib (6 to 9 months). Increased ALT was observed in monkeys, and increased AST and/or decreased albumin were observed in rats and monkeys.

In clinical studies, 4 cases of hepatotoxicity, 2 cases of cytolytic hepatitis, 1 case of hepatic steatosis and 1 case of hepatitis were observed

### **Renal Impairment**

There are currently no clinical studies with SPRYCEL in patients with impaired renal function (clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range). Dasatinib and its metabolites are minimally excreted via the kidney. Since the renal excretion of unchanged dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency. The effect of dialysis on dasatinib pharmacokinetics has not been studied.

## **Rhabdomyolysis**

Cases of rhabdomyolysis with acute renal failure have been reported. Patients with muscle symptoms (muscle aches/pains) should be investigated to rule out rhabdomyolysis (elevated creatine kinase, elevated serum creatinine, hyperkalemia, hyperphosphatemia, brown urine, elevated ALT and AST).

## **Carcinogenesis and Mutagenesis**

Carcinogenicity studies were not performed with dasatinib.

Dasatinib was clastogenic *in vitro* to dividing Chinese hamster ovary cells with and without metabolic activation at concentrations ranging from 5 to 60 µg/mL. Dasatinib was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

## **Drug-Drug Interaction**

**CYP3A4 inhibitors:** Concomitant use of dasatinib and medicinal products that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grape fruit juice) may increase exposure to dasatinib. Therefore, in patients receiving SPRYCEL, coadministration of a potent CYP3A4 inhibitor is not recommended. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction to 20 or 40 mg daily should be considered (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

**CYP3A4 inducers:** Concomitant use of dasatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. In addition, more healthy male subjects experienced increases in QTcF of > 30 msec from the baseline ECG recordings when dasatinib and rifampicin were administered 12 hours apart compared to when dasatinib was administered alone (25% vs. 10%). No subject experienced QTcF > 450 msec or a change from baseline > 60 msec. (see DRUG INTERACTIONS). Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used.

**CYP3A4 substrates:** Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In addition, three healthy subjects (n = 48) experienced increases in QTcF of > 30 msec from the baseline ECG recordings following concomitant use of a single dose of dasatinib and simvastatin. No subject experienced QTcF > 450 msec or a change from baseline > 60 msec (see DRUG INTERACTIONS). Therefore, caution is warranted when SPRYCEL is co-administered with a drug that potentially alters CYP3A4 activity, a QTc prolonger, or CYP3A4 substrates of narrow therapeutic index such as macrolide antibiotics, benzodiazepine, pimozide, quinidine, or ergot alkaloids (ergotamine, dihydroergotamine). The

effect of a CYP3A4 substrate on the pharmacokinetic parameters of dasatinib has not been studied.

H2 antagonists or proton pump inhibitors: Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure (see DRUG INTERACTIONS). **The use of antacids should be considered in place of H2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.**

Antacids: Concomitant use of dasatinib and aluminum hydroxide/magnesium hydroxide may reduce exposure to dasatinib. However, **aluminum hydroxide/magnesium hydroxide products may be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib** (see DRUG INTERACTIONS).

Antiemetics: No information is available on the safety of concomitant use of dasatinib with antiemetics (prochlorperazine, metochlopramide, 5-HT3 inhibitors).

### *Lactose*

SPRYCEL tablets 20 mg, 50 mg, 70 mg and 100 mg contain lactose in proportional amounts of 27 mg, 67.5 mg, 94.5 mg and 135 mg, respectively. SPRYCEL therefore contains 189 mg of lactose in the 140 mg daily dose of dasatinib and 135 mg in the 100 mg daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take dasatinib.

### **Special Populations:**

*Pregnant Women:* There are no adequate data from the use of dasatinib in pregnant women. Studies in animals have shown that at concentrations which are readily achievable in humans receiving therapeutic doses of SPRYCEL, fetal toxicity was observed in both pregnant rats and rabbits. Fetal death was observed in rats (see TOXICOLOGY). The potential risk for humans is unknown.

SPRYCEL is, therefore, not recommended for use in women who are pregnant or contemplating pregnancy. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus.

*Nursing Women:* It is unknown whether SPRYCEL is excreted in human milk. Women who are taking SPRYCEL should not breastfeed.

*Pediatrics (<18 years of age):* The safety and efficacy of SPRYCEL in patients <18 years of age have not been established.

*Geriatrics (> 65 years of age):* Of the 2182 patients in clinical studies of SPRYCEL, 547 (25%) were 65 years of age and older and 105 (5%) were 75 years of age and older. While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention, congestive heart

failure, gastrointestinal bleeding and dyspnea events and should be monitored closely. No differences in efficacy were observed between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and older (42% MCyR in patients  $\geq$  65 years versus 56% MCyR in the rest of the study population and 47% MCyR in patients  $\geq$  65 years versus 68% MCyR in the rest of the study population in studies CA180017 and CA180034, respectively).

### **Sexual Function/Reproduction**

The effects of SPRYCEL on male and female fertility are not known. The potential effects of SPRYCEL on sperm have not been studied. Sexually active male or female patients taking SPRYCEL should use adequate contraception.

### **Monitoring and Laboratory Tests**

Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. (see WARNINGS AND PRECAUTIONS: Myelosuppression). Hepatic function tests (AST, ALT and bilirubin), CK and renal function tests should be performed every two weeks for the first 2 months and then monthly thereafter or as clinically indicated (see WARNINGS AND PRECAUTIONS: Hepatic Impairment and Rhabdomyolysis).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The data described below reflect exposure to SPRYCEL in 2182 patients with leukemia in clinical studies (1850 patients treated with 140 mg once daily or 70 mg twice daily and 332 patients treated with 50 mg twice daily or 100 mg once daily). The median duration of therapy was 15 months (range < 1 - 31 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Most reactions were mild to moderate. SPRYCEL was discontinued due to study drug toxicity in 8-15% of patients in all stages of CML or Ph+ ALL.

The most frequently reported adverse events, in the pooled safety data of 2182 patients, regardless of causality or severity, were diarrhea, fluid retention, headache, musculoskeletal pain, hemorrhage, pyrexia, fatigue, infection, skin rash, nausea, dyspnea, cough, upper respiratory tract infection/inflammation, vomiting, pain and abdominal pain.

### **Clinical Trial Adverse Drug Reactions in patients treated with SPRYCEL**

All treatment-emergent adverse events (excluding laboratory abnormalities), regardless of relationship to study drug, that were reported in at least 5% of the patients treated with

SPRYCEL in clinical studies are shown in Table 1 for chronic phase CML and Table 2 for advanced phase CML and Ph+ALL.

In the Phase III dose-optimization study exploring lower doses of SPRYCEL (100 mg/day) in patients with chronic phase CML, the median duration of therapy was approximately 22 months (range <1–30 months). In the Phase III dose-optimization study exploring the once daily schedule of SPRYCEL (140 mg once daily) in patients with advanced diseases, the median duration of therapy was 13.62 months (range .03–31.15 months) for accelerated phase CML, 3.19 months (range .03–27.73 months) for myeloid blast CML, 3.55 months (range .10–22.08 months) for lymphoid blast CML, and 2.99 months (range .16–23.46 months) for Ph+ ALL.

**Table 1: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Chronic Phase CML (Recommended Starting Dose: 100 mg Once Daily)**

Preferred Term	Phase III								All Other	
	100 mg QD n=165		50 mg BID <sup>a</sup> n=167		140 mg QD <sup>a</sup> n=163		70 mg BID <sup>a</sup> n=167		70 mg BID <sup>a</sup> n=488	
	Percent (%) of Patients									
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Headache	45	1	35	1	45	4	46	4	46	2
Musculoskeletal pain	45	3	31	2	44	2	35	5	46	3
Infection (including bacterial, viral, fungal, non-specified)	42	5	36	2	39	4	37	4	47	7
Upper respiratory tract infection/inflammation	40	1	47	2	31	0	32	1	47	2
Diarrhea	38	3	42	5	43	4	46	7	51	4
Fluid Retention	33	5	38	5	45	9	43	11	57	14
Superficial edema	21	0	24	0	21	1	26	1	36	<1
Pleural effusion	14	2	23	4	26	5	25	6	34	9
Generalized edema	4	1	0	0	6	0	1	0	6	1
Congestive heart failure/cardiac dysfunction <sup>b</sup>	2	1	1	1	5	2	7	3	6	4
Pericardial effusion	2	1	6	2	6	2	2	1	5	1
Pulmonary edema	1	0	1	1	0	0	3	1	3	1
Ascites	0	0	0	0	0	0	0	0	<1	0
Pulmonary hypertension	0	0	1	0	1	0	2	1	2	1
Fatigue	34	2	31	0	37	2	25	4	47	4
Cough	30	1	30	0	26	1	31	0	37	1
Skin rash	29	2	32	2	37	1	31	2	44	1
Arthralgia	27	2	22	2	25	1	20	4	28	2

**Table 1: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Chronic Phase CML (Recommended Starting Dose: 100 mg Once Daily)**

Preferred Term	Phase III								All Other	
	100 mg QD n=165		50 mg BID <sup>a</sup> n=167		140 mg QD <sup>a</sup> n=163		70 mg BID <sup>a</sup> n=167		70 mg BID <sup>a</sup> n=488	
	Percent (%) of Patients									
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Dyspnea	27	2	29	7	31	8	28	6	44	7
Pain	25	1	22	2	24	1	23	1	30	1
Hemorrhage	23	3	23	4	29	2	26	2	33	3
Gastrointestinal bleeding	5	1	8	4	5	1	6	2	7	2
CNS bleeding	0	0	1	0	1	0	0	0	1	0
Nausea	22	1	29	1	32	1	39	2	37	1
Abdominal pain	19	1	24	1	26	4	20	2	29	2
Pyrexia	18	1	26	1	26	0	25	1	37	2
Constipation	16	2	14	1	12	0	10	0	15	<1
Myalgia	16	0	11	0	17	1	12	1	17	1
Chest pain	15	2	14	4	14	1	13	1	17	1
Dizziness	14	1	12	0	15	1	14	2	19	<1
Pruritus	14	1	10	0	13	0	11	0	14	0
Vomiting	14	1	18	2	20	2	29	1	20	1
Neuropathy (including peripheral neuropathy)	12	1	14	1	14	0	10	1	19	1
Pneumonia (including bacterial, viral, and fungal)	11	4	11	4	10	6	14	6	11	5
Hyperhidrosis	10	0	8	0	7	0	5	0	13	0
Insomnia	10	0	6	0	12	0	6	0	11	0
Mucosal inflammation (including mucositis/stomatitis)	10	0	14	0	10	1	11	1	14	<1
Weight increased	10	1	7	1	5	0	6	1	11	<1
Abdominal distension	10	0	8	0	7	0	5	0	13	0
Arrhythmia (including tachycardia)	8	0	6	1	9	1	7	2	11	2
Asthenia	8	1	13	1	9	1	14	0	20	1
Dyspepsia	8	0	7	1	16	0	12	0	11	0
Palpitations	8	0	4	0	2	0	7	0	5	0

**Table 1: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Chronic Phase CML (Recommended Starting Dose: 100 mg Once Daily)**

Preferred Term	Phase III								All Other	
	100 mg QD n=165		50 mg BID <sup>a</sup> n=167		140 mg QD <sup>a</sup> n=163		70 mg BID <sup>a</sup> n=167		70 mg BID <sup>a</sup> n=488	
	Percent (%) of Patients									
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Anorexia	7	0	11	2	9	0	13	1	19	<1
Chills	7	0	10	0	7	0	7	0	10	0
Depression	7	1	8	2	7	1	5	1	8	1
Visual disorder	7	0	4	0	4	0	5	0	7	0
Weight decreased	7	0	10	0	12	1	14	1	16	1
Alopecia	6	0	3	0	4	0	7	0	10	0
Enterocolitis infection	6	1	7	1	4	1	8	1	6	1
Hypertension	6	0	6	1	6	1	9	2	8	<1
Urinary frequency	6	1	5	0	7	0	5	0	5	<1
Dry skin	5	0	2	0	3	0	3	0	7	0
Muscle inflammation	5	0	10	1	3	0	5	0	10	<1
Acne	5	0	8	1	9	0	10	0	9	<1
Flushing	4	0	4	0	6	0	7	0	9	0
Hypersensitivity (including erythema nodosum)	4	1	1	0	7	2	3	1	4	1
Anxiety	4	0	8	2	6	0	7	0	7	0
Herpes virus infection	4	1	2	0	6	0	5	1	5	<1
Contusion	2	0	7	0	6	0	2	0	7	0
Gastritis	2	0	5	1	7	1	5	1	6	1
Musculoskeletal stiffness	1	0	5	0	2	0	2	0	4	0

<sup>a</sup> Not a recommended starting dosage of SPRYCEL for chronic phase CML. Data provided for context with the dose optimization trial

<sup>b</sup> Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure.

**Table 2: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Advanced Phase CML and Ph+ALL (Recommended Starting Dose: 140 mg Once Daily)**

Preferred Term	Phase III				All Other	
	140 mg QD n = 304		70 mg BID <sup>a</sup> n = 305		70 mg BID <sup>a</sup> n = 423	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
	Percent (%) of Patients					
Infection	45	14	38	12	51	13
Diarrhea	44	6	49	6	63	10
Hemorrhage	43	12	39	12	59	21
Gastrointestinal bleeding	16	8	18	9	26	13
CNS bleeding	4	1	4	1	4	2
Fluid Retention	42	8	50	12	65	16
Superficial oedema	25	<1	26	2	48	2
Pleural Effusion	24	7	36	8	37	10
Generalised oedema	2	0	5	1	10	1
Congestive heart failure/ cardiac dysfunction <sup>b</sup>	3	1	4	2	5	3
Pericardial effusion	2	1	7	2	10	2
Pulmonary oedema	2	1	4	2	6	1
Ascites	<1	<1	1	0	4	1
Pulmonary hypertension	<1	0	2	<1	3	1
Pyrexia	38	3	37	3	59	10
Headache	37	4	33	4	43	4
Musculoskeletal pain	36	7	34	6	50	8
Nausea	33	2	30	3	42	2
Fatigue	29	5	30	5	42	6
Vomiting	27	1	27	3	37	3
Dyspnea	27	6	32	9	40	11
Cough	27	0	30	0	37	1
Skin Rash	26	<1	27	2	41	2
Upper respiratory tract infection/inflammation	24	1	24	1	31	3
Pain	23	2	19	1	36	4
Arthralgia	21	2	17	2	23	2

**Table 2: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Advanced Phase CML and Ph+ALL (Recommended Starting Dose: 140 mg Once Daily)**

Preferred Term	Phase III				All Other	
	140 mg QD n = 304		70 mg BID <sup>a</sup> n = 305		70 mg BID <sup>a</sup> n = 423	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Percent (%) of Patients						
Abdominal pain	19	4	18	3	35	4
Weight decreased	16	1	16	2	22	2
Mucosal inflammation (including mucositis/stomatitis)	16	1	16	1	26	2
Pneumonia (including bacterial, viral, and fungal)	15	9	17	8	21	11
Constipation	15	1	12	0	20	<1
Anorexia	14	1	21	2	26	2
Neuropathy (including peripheral neuropathy)	13	1	10	<1	16	<1
Arrhythmia (including tachycardia)	13	1	10	1	16	2
Asthenia	12	2	11	3	22	5
Chest pain	12	1	9	1	16	2
Febrile neutropenia	11	11	13	13	17	16
Myalgia	11	1	10	1	16	1
Weight increased	10	1	10	1	22	2
Hyperhidrosis	9	0	7	0	12	0
Pruritus	9	0	9	1	13	0
Dizziness	8	1	9	<1	17	0
Dyspepsia	8	0	5	0	12	<1
Depression	7	0	8	<1	10	<1
Hypertension	7	1	7	2	8	1
Hypotension	6	2	5	1	9	3
Insomnia	6	0	7	0	11	<1
Sepsis (including fatal outcomes)	6	4	10	7	12	9
Anxiety	6	1	6	<1	10	<1
Contusion	6	<1	2	0	8	0
Dry skin	6	0	4	0	7	0
Lung infiltration	5	2	3	1	6	3
Renal failure	5	4	2	1	5	4

**Table 2: Adverse Events Reported in ≥5% of Patients in Clinical Studies of Advanced Phase CML and Ph+ALL (Recommended Starting Dose: 140 mg Once Daily)**

Preferred Term	Phase III				All Other	
	140 mg QD n = 304		70 mg BID <sup>a</sup> n = 305		70 mg BID <sup>a</sup> n = 423	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Percent (%) of Patients						
Abdominal distension	5	<1	8	0	16	0
Colitis (including neutropenic colitis)	5	3	6	2	8	3
Enterocolitis infection	5	1	3	2	7	2
Visual disorder	4	<1	4	<1	7	1
Chills	4	0	7	<1	16	<1
Herpes virus infection	4	1	2	<1	8	1
Oral soft tissue disorder	4	0	1	0	8	0
Somnolence	4	1	6	1	4	<1
Urinary frequency	4	0	4	<1	6	<1
Gastritis	4	1	4	1	5	<1
Pneumonitis	4	2	3	1	6	2
Acne	3	0	2	0	6	0
Flushing	3	0	5	0	10	0
Alopecia	2	0	6	0	6	0

a Not a recommended starting dosage of SPRYCEL for advanced phase CML and Ph+ALL. . Data provided for context with the dose optimization trial.

b Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

In a Phase II randomized study of chronic phase CML, 101 patients received SPRYCEL (starting dosage 70 mg twice daily) and 49 patients received imatinib (starting dosage 800 mg daily). Crossover to the alternate therapy was permitted in this study. The median duration of therapy prior to crossover was longer for SPRYCEL than for imatinib (see CLINICAL TRIALS). Selected adverse events, regardless of relationship to study drug, are presented in Table 3.

**Table 3: Selected Adverse Events in Phase II Randomized Study (Chronic Phase CML)**

Preferred Term	SPRYCEL <sup>a</sup> n=101		Imatinib <sup>a</sup> n=49	
	All Grades	Grade 3/4	All Grades	Grade 3/4
	Percent (%) of Patients			
Nausea	32	0	39	0
Pleural Effusion	26	5	0	0
Superficial Edema	26	1	47	0
Vomiting	18	0	27	0
Congestive Heart Failure/Cardiac Dysfunction <sup>b</sup>	3	2	0	0

a Starting dosage: SPRYCEL 70 mg twice daily; imatinib 800 mg daily.

b Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

**Less Common Clinical Trial Adverse Drug Reactions (<5% all grades) reported in Clinical Trials in patients treated with SPRYCEL**

The following adverse reactions, regardless of relationship to therapy or dosing regimen, were reported in patients in the SPRYCEL clinical studies at a frequency of <5%. These reactions are presented by frequency category. Frequent reactions are those occurring in ≥1% of patients, infrequent reactions are those occurring in 0.1% – <1% of patients and rare reactions are those occurring in <0.1% of patients. These events are included based on clinical relevance.

**Gastrointestinal Disorders:** *Frequent:* dysphagia; *Infrequent:* anal fissure, esophagitis, upper gastrointestinal ulcer, pancreatitis, ileus.

**General Disorders and Administration Site Conditions:** *Frequent:* malaise; *Infrequent:* temperature intolerance.

**Musculoskeletal and Connective Tissue Disorders:** *Frequent:* muscular weakness; *Infrequent:* tendonitis, rhabdomyolysis.

**Nervous System Disorders:** *Frequent:* dysgeusia, syncope, amnesia, tremor, convulsion; *Infrequent:* cerebrovascular accident, transient ischemic attack; *Rare:* reversible posterior leukoencephalopathy syndrome.

**Respiratory, Thoracic, and Mediastinal Disorders:** *Frequent:* asthma; *Infrequent:* bronchospasm, acute respiratory distress syndrome.

**Skin and Subcutaneous Tissue Disorders:** *Frequent:* dermatitis including eczema, urticaria, skin ulcer, pigmentation disorder, photosensitivity; *Infrequent:* bullous conditions, nail disorder, acute febrile neutrophilic dermatosis, palmar-plantar erythrodysesthesia syndrome, panniculitis.

**Vascular Disorders:** *Frequent:* thrombophlebitis; *Rare:* livedo reticularis.

**Investigations:** *Infrequent:* blood creatine phosphokinase increased; *Rare:* platelet aggregation abnormal.

**Metabolism and Nutrition Disorders:** *Frequent:* appetite disturbances, hyperuricemia; *infrequent:* hypoalbuminemia.

**Cardiac Disorders:** *Frequent:* angina pectoris, cardiomegaly; *Infrequent:* electrocardiogram QT prolonged, myocardial infarction, pericarditis, ventricular arrhythmia (including ventricular tachycardia), myocarditis; *Rare:* acute coronary syndrome, cor pulmonale.

**Psychiatric Disorders:** *Frequent:* confusional state, affect lability; *Infrequent:* libido decreased.

**Blood and Lymphatic System Disorders:** *Frequent:* pancytopenia; *Infrequent:* coagulopathy; *Rare:* aplasia pure red cell.

**Eye Disorders:** *Frequent:* conjunctivitis, dry eye.

**Renal and Urinary Disorders:** *Infrequent:* proteinuria.

**Ear and Labyrinth Disorders:** *Frequent:* tinnitus, vertigo.

**Reproductive System and Breast Disorders:** *Frequent:* gynecomastia; *Infrequent:* menstruation irregular.

**Hepatobiliary Disorders:** *Infrequent:* cholecystitis, cholestasis, hepatitis.

**Neoplasms Benign, Malignant and Unspecified:** *Infrequent:* tumor lysis syndrome.

## **Abnormal Hematologic and Clinical Chemistry Findings**

Myelosuppression was commonly reported in all studies. However, the frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. Most patients continued treatment without further progressive myelosuppression.

In patients who experienced severe myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions. Occasionally permanent discontinuation of treatment was required.

Elevations of transaminases or bilirubin were reported in all disease phases, but were more common in patients with advanced disease. The numbers of patients who developed three or more simultaneous significant elevations of transaminases or bilirubin suggestive of hepatic toxicity were as follows: Chronic phase, 4; accelerated, 13; myeloid blast, 13; lymphoid blast, 7. Most events were managed with dose reduction or interruption. One patient required discontinuation of treatment due to abnormalities of liver function tests. Although causality has

not been established, the occurrence of abnormal liver function tests on treatment should be followed closely and consideration given to discontinuing SPRYCEL.

**Hypocalcemia:**

Between 48% and 76% of patients experienced hypocalcemia at least once during this period. Grade 3 or 4 abnormalities were reported in 2, 7, 16, 13 and 9% of the patients in the chronic phase CML (n=1150), accelerated phase CML (n=502), myeloid blast phase CML (n=280), lymphoid blast phase CML (n=115) and Ph+ ALL (n=135), respectively. The percentage of patients with hypocalcemia who were treated with calcium supplements is 7% for chronic phase CML, 16% for accelerated phase CML, 28% for myeloid blast CML, 20% for lymphoid blast CML and 20% for Ph+ALL.

**Hypophosphatemia:**

Between 41% and 50% of patients experienced hypophosphatemia at least once during this period. Grade 3 or 4 abnormalities were reported in 10, 13, 20, 19 and 21% of the patients in the chronic phase CML (n=1150), accelerated phase CML (n=502), myeloid blast phase CML (n=280), lymphoid blast phase CML (n=115) and Ph+ ALL (n=135), respectively.

In the Phase II randomized study, the frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was 63%, 57%, and 20%, respectively, in the SPRYCEL group and 39%, 14%, and 8%, respectively, in the imatinib group. The frequency of Grade 3 or 4 hypocalcemia was 5% in the SPRYCEL group and 0% in the imatinib group. Laboratory abnormalities are shown in Table 4 for chronic phase CML and in Table 5 for advanced phase CML and Ph+ALL.

**Table 4: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies of Chronic Phase CML (Recommended Starting Dose: 100 mg Once Daily)**

	Phase III				All Other
	100 mg QD n=165	50 mg BID <sup>a</sup> n=167	140 mg QD <sup>a</sup> n=163	70 mg BID <sup>a</sup> n=167	70 mg BID <sup>a</sup> n=488
<b>Percent (%) of Patients</b>					
<b>Hematology Parameters</b>					
Neutropenia	35	47	44	45	53
Thrombocytopenia	23	36	41	38	51
Anemia	13	18	19	18	22
<b>Biochemistry Parameters</b>					
Hypophosphatemia	10	8	6	9	13
Hypokalemia	2	2	4	4	4
Hypocalcemia	1	0	2	3	3
Elevated SGPT (ALT)	0	1	1	1	1

**Table 4: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies of Chronic Phase CML (Recommended Starting Dose: 100 mg Once Daily)**

	Phase III				All Other
	100 mg QD n=165	50 mg BID <sup>a</sup> n=167	140 mg QD <sup>a</sup> n=163	70 mg BID <sup>a</sup> n=167	70 mg BID <sup>a</sup> n=488
<b>Percent (%) of Patients</b>					
Elevated SGOT (AST)	1	1	1	0	1
Elevated Bilirubin	1	0	1	1	1
Elevated Creatinine	0	0	1	1	1

<sup>a</sup> Not a recommended starting dosage of SPRYCEL for chronic phase CML. Data provided for context with dose optimization trial.

CTC grades: neutropenia (Grade 3  $\geq 0.5$ – $< 1.0 \times 10^9/L$ , Grade 4  $< 0.5 \times 10^9/L$ ); thrombocytopenia (Grade 3  $\geq 25$ – $< 50 \times 10^9/L$ , Grade 4  $< 25 \times 10^9/L$ ); anemia (hemoglobin Grade 3  $\geq 65$ – $< 80$  g/L, Grade 4  $< 65$  g/L); elevated creatinine (Grade 3  $> 3$ – $6 \times$  upper limit of normal range (ULN), Grade 4  $> 6 \times$  ULN); elevated bilirubin (Grade 3  $> 3$ – $10 \times$  ULN, Grade 4  $> 10 \times$  ULN); elevated SGOT or SGPT (Grade 3  $> 5$ – $20 \times$  ULN, Grade 4  $> 20 \times$  ULN); hypocalcemia (Grade 3  $< 7.0$ – $6.0$  mg/dL, Grade 4  $< 6.0$  mg/dL); hypophosphatemia (Grade 3  $< 2.0$ – $1.0$  mg/dL, Grade 4  $< 1.0$  mg/dL); hypokalemia (Grade 3  $< 3.0$ – $2.5$  mmol/L, Grade 4  $< 2.5$  mmol/L).

**Table 5: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies of Advanced Phase CML and Ph+ALL (Recommended Starting Dose: 140 mg Once Daily)**

	Phase III		All Other
	140 mg QD n = 304	70 mg BID <sup>a</sup> n = 305	70 mg BID <sup>a</sup> n = 423
<b>Percent (%) of Patients</b>			
<b>Preferred Term</b>			
<b>Hematology Parameters</b>			
Neutropenia	67	72	81
Thrombocytopenia	71	71	83
Anemia	54	51	67
<b>Biochemistry Parameters</b>			
Hypophosphatemia	14	14	21
Hypokalemia	9	14	17
Hypocalcemia	6	9	14
Elevated SGPT (ALT)	4	3	8
Elevated SGOT (AST)	2	1	5
Elevated Bilirubin	3	2	4
Elevated Creatinine	3	1	1

<sup>a</sup> Not a recommended starting dosage of SPRYCEL for advanced phase CML and Ph+ALL. Data provided for context with dose optimization trial.

CTC grades: neutropenia (Grade 3  $\geq 0.5$ – $< 1.0 \times 10^9/L$ , Grade 4  $< 0.5 \times 10^9/L$ ); thrombocytopenia (Grade 3  $\geq 25$ – $< 50 \times 10^9/L$ , Grade 4  $< 25 \times 10^9/L$ ); anemia (hemoglobin Grade 3  $\geq 65$ – $< 80$  g/L, Grade 4  $< 65$  g/L); elevated creatinine (Grade 3  $> 3$ – $6 \times$  upper limit of normal range (ULN), Grade 4  $> 6 \times$  ULN); elevated bilirubin (Grade 3  $> 3$ – $10 \times$  ULN, Grade 4  $> 10 \times$  ULN); elevated SGOT or SGPT (Grade 3  $> 5$ – $20 \times$  ULN, Grade 4  $> 20 \times$  ULN); hypocalcemia (Grade 3  $< 7.0$ – $6.0$  mg/dL, Grade 4  $< 6.0$  mg/dL); hypophosphatemia (Grade 3  $< 2.0$ – $1.0$  mg/dL, Grade 4  $< 1.0$  mg/dL); hypokalemia (Grade 3  $< 3.0$ – $2.5$  mmol/L, Grade 4  $< 2.5$  mmol/L).

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

<b>Cardiac disorders:</b>	atrial fibrillation/atrial flutter <sup>a</sup>
<b>Vascular disorders:</b>	thrombosis/embolism (including pulmonary embolism, deep vein thrombosis) <sup>b</sup>
<b>Respiratory, thoracic and mediastinal disorders:</b>	interstitial lung disease
<b>Gastrointestinal disorders:</b>	fatal gastrointestinal hemorrhage <sup>c</sup>

- Typically reported in elderly patients or in patients with confounding factors including significant underlying or concurrent cardiac or cardiovascular disorders, or other significant comorbidities (eg, severe infection/sepsis, electrolyte abnormalities).
- Typically reported in patients with underlying malignancies or other confounding or risk factors, including cardiovascular disorders, history of surgery, or other comorbidities.
- Typically reported in patients with progressive underlying malignancies (eg, advanced phase of CML or Ph+ ALL) or severe or life-threatening comorbidities (eg, severe gastrointestinal disorders, infection or sepsis, thrombocytopenia).

## DRUG INTERACTIONS

### Overview

Dasatinib is not an inducer of human CYP enzymes. Dasatinib is an inhibitor of CYP3A4 and may decrease the metabolic clearance of drugs that are primarily metabolized by CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1.

### Drug-Drug Interactions

#### *Drugs that may increase dasatinib plasma concentrations*

**CYP3A4 Inhibitors:** *In vitro* studies indicate that dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg SPRYCEL once daily coadministered with 200 mg of ketoconazole BID increased the dasatinib C<sub>max</sub> and AUC by four- and five-fold, respectively. Substances that inhibit CYP3A4 activity (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, grape fruit juice) may decrease metabolism and increase concentrations of dasatinib (see WARNINGS AND PRECAUTIONS: Drug Interactions Interactions and DOSAGE AND ADMINISTRATION).

#### *Drugs that may decrease dasatinib plasma concentrations*

**CYP3A4 Inducers:** Data from a study of 20 healthy subjects indicate that when a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampicin, a potent CYP3A4 inducer, the mean C<sub>max</sub> and AUC of dasatinib were

decreased by 81% and 82%, respectively. In addition, more healthy male subjects experienced increases in QTcF of > 30msec from the baseline recordings when a single dose of dasatinib was administered 12 hours following rifampicin compared to when dasatinib was given alone (25% vs. 10%, n = 20). No subject experienced QTcF > 450 msec or a change from baseline  $\geq$  60 msec (see WARNINGS AND PRECAUTIONS: Cardiovascular, Drug-Drug Interaction and TOXICOLOGY: Safety Pharmacology).

**Antacids:** Nonclinical data indicate that dasatinib has pH dependent solubility. In a study of 24 healthy subjects, administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single 50 mg dose of SPRYCEL was associated with no relevant change in dasatinib AUC or C<sub>max</sub>. On the contrary, when 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50 mg dose of SPRYCEL, a 55% reduction in dasatinib AUC and a 58% reduction in C<sub>max</sub> were observed (See WARNINGS AND PRECAUTIONS: Drug-Drug Interaction.).

**Famotidine:** In a study of 24 healthy subjects, administration of a single 50 mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and C<sub>max</sub> of SPRYCEL by 61% and 63%, respectively (See WARNINGS AND PRECAUTIONS: Drug-Drug Interaction).

*Drugs that may have their plasma concentration altered by dasatinib*

**CYP3A4 Substrates:** Single dose data from a study of 54 healthy subjects indicate that the mean C<sub>max</sub> and AUC of simvastatin, a prototypical CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin (80 mg) was administered in combination with a single 100 mg dose of SPRYCEL. In addition, three healthy subjects (n = 48) experienced QTcF of > 30 msec from the baseline ECG recordings following the concomitant use of a single dose of simvastatin and dasatinib. No subject experienced QTcF > 450 msec or a change from baseline > 60 msec. The effect of CYP3A4 substrates on the pharmacokinetics of dasatinib has not been studied (See WARNINGS AND PRECAUTIONS: Cardiovascular, Drug-Drug Interaction).

## **DOSAGE AND ADMINISTRATION**

Current dosing recommendations are based on the results of two randomized Phase III dose-optimization studies in patients with chronic and advanced phases CML and Ph+ALL (see CLINICAL TRIALS section).

- The recommended starting dosage of SPRYCEL (dasatinib) for chronic phase CML is 100 mg administered orally once daily (OD), either in the morning or in the evening.
- The recommended starting dosage of SPRYCEL for accelerated phase CML, or myeloid or lymphoid blast CML, is 140 mg/day administered orally once daily (140 mg QD) either in the morning or in the evening.
- The recommended starting dosage of SPRYCEL for Ph+ALL is 140 mg administered orally once daily (140 mg QD) either in the morning or in the evening.

SPRYCEL can be taken with or without food. Tablets should not be crushed or cut; they should be swallowed as a whole.

In clinical studies, treatment with SPRYCEL was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a complete cytogenetic response (CCyR) has not been investigated.

CYP3A4 inhibitors such as ketoconazole may **increase** SPRYCEL plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease to 20 or 40 mg daily should be considered (see WARNINGS AND PRECAUTIONS: Drug Interactions and DRUG INTERACTIONS).

### Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended dosage.

### Dose Adjustment for Adverse Reactions

#### *Myelosuppression*

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 6.

**Table 6: Dose Adjustments for Neutropenia and Thrombocytopenia**

<p>Chronic Phase CML (starting dose 100 mg once daily)</p>	<p>ANC* <math>&lt;0.5 \times 10^9/L</math> and/or Platelets <math>&lt;50 \times 10^9/L</math></p>	<ol style="list-style-type: none"> <li>1. Stop SPRYCEL until ANC <math>\geq 1.0 \times 10^9/L</math> and platelets <math>\geq 50 \times 10^9/L</math>.</li> <li>2. Resume treatment with SPRYCEL at the original starting dose.</li> <li>3. If platelets <math>&lt;25 \times 10^9/L</math> and/or recurrence of ANC <math>&lt;0.5 \times 10^9/L</math> for <math>&gt;7</math> days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode)</li> </ol>
<p>Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)</p>	<p>ANC* <math>&lt;0.5 \times 10^9/L</math> and/or Platelets <math>&lt;10 \times 10^9/L</math></p>	<ol style="list-style-type: none"> <li>1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy).</li> <li>2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC <math>\geq 1.0 \times 10^9/L</math> and platelets <math>\geq 20 \times 10^9/L</math> and resume at the original starting dose.</li> <li>3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).</li> <li>4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.</li> </ol>

\*ANC: absolute neutrophil count

### *Non-hematological adverse reactions*

If a severe non-hematological adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

Pediatrics (< 18 years of age): SPRYCEL is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy

**Hepatic impairment:** No clinical pharmacokinetic trials were conducted with a 70-100 mg dose of SPRYCEL in patients with decreased liver function. SPRYCEL should be used with caution in patients with moderate to severe hepatic impairment (see WARNINGS AND PRECAUTIONS).

**Renal impairment:** No clinical trials were conducted with SPRYCEL in patients with decreased renal function (trials excluded patients with serum creatinine concentration > 1.5 times the upper limit of the normal range). Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

### **OVERDOSAGE**

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest reported dosage ingested was 280 mg per day for 1 week in two patients and both developed a significant decrease in platelet counts. Since SPRYCEL is associated with severe myelosuppression (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS), patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases (LYN, HCK), along with a number of other kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGF $\beta$  receptor. Dasatinib is a potent inhibitor of the BCR-ABL and SRC family kinases with potency at sub-nanomolar concentrations. It binds not only to the inactive but also to the active conformation of the enzyme.

### Pharmacodynamics

*In vitro*, dasatinib is active in leukemic cell lines representing variants of imatinib sensitive and resistant disease. These nonclinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations (14/15 mutations with exception of T315I), activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene, *MDR1*, overexpression.

*In vivo*, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient-derived CML cell lines (see DETAILED PHARMACOLOGY).

### Pharmacokinetics

The pharmacokinetics of SPRYCEL (dasatinib) were evaluated in 229 healthy subjects and in 84 patients with leukemia.

*Absorption:* Dasatinib is rapidly absorbed in patients following oral administration. Peak concentrations were observed between 0.5-3 hours. The overall mean terminal half-life of dasatinib is approximately 5-6 hours.

*Distribution:* In patients, SPRYCEL has a large apparent volume of distribution (2505 L) suggesting that the drug is extensively distributed in the extravascular space.

*Metabolism:* Dasatinib is extensively metabolized in humans. In a study of 8 healthy subjects administered 100 mg of [ $^{14}$ C]-labeled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the drug. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

*Excretion:* Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [ $^{14}$ C]-labeled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the administered radioactivity recovered in the urine and feces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

## **Special Populations and Conditions:**

*Pediatrics:* No clinical studies were conducted with SPRYCEL in pediatric populations.

*Hepatic Insufficiency:* The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic impaired subjects who received a 50-mg dose and 5 severely hepatic-impaired subjects who received a 20-mg dose compared to matched healthy subjects who received a 70-mg dose of SPRYCEL. The mean C<sub>max</sub> and AUC of dasatinib adjusted for the 70-mg dose was decreased by 47% and 8%, respectively, in moderate hepatic impairment compared to subjects with normal hepatic function. In severe hepatic impaired subjects, the mean C<sub>max</sub> and AUC adjusted for the 70-mg dose was decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function. Hepatic impairment did not result in clinically meaningful change in dasatinib exposure at the doses studied. However no pharmacokinetic information is available from patients with hepatic impairment treated with a 70-100 mg dose of SPRYCEL. Due to limitations of this clinical study, caution is recommended in patients with hepatic impairment (See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

*Renal Insufficiency:* No clinical studies were conducted with SPRYCEL in patients with decreased renal function. Less than 4% of SPRYCEL and its metabolites are excreted via the kidney. (See WARNINGS AND PRECAUTIONS.)

*Electrocardiogram:* In five Phase II clinical studies in patients with leukemia, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving SPRYCEL 70 mg BID. QT interval was corrected for heart rate by Fridericia's method. At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4-6 msec, with associated upper 95% confidence intervals <7 msec and lower 95% confidence intervals > -2 msec. Of the 2182 patients who received SPRYCEL in clinical trials, 21 patients (<1%) experienced a QTcF >500 msec. (See WARNINGS AND PRECAUTIONS.)

## **Drug-Drug Interactions**

See DRUG INTERACTIONS section.

## **Drug-Food Interactions**

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure.

## **STORAGE AND STABILITY**

SPRYCEL (dasatinib) tablets should be stored at room temperature between 15°–30° C.

## **SPECIAL HANDLING INSTRUCTIONS**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

SPRYCEL (dasatinib) tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However, if tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING.**

SPRYCEL (dasatinib) film coated tablets are available for oral administration in strengths 20 mg, 50 mg, 70 mg and 100 mg dasatinib (as monohydrate) containing the following non-medicinal ingredients for the tablet core: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating contain the following inactive ingredients: hypromellose, polyethylene glycol and titanium dioxide.

SPRYCEL 20 mg tablet is white to off-white, biconvex, round, film coated tablet with “BMS” debossed on one side and “527” on the other.

SPRYCEL 50 mg tablet is white to off-white, biconvex, oval, film coated tablet with “BMS” debossed on one side and “528” on the other side.

SPRYCEL 70 mg tablet is white to off-white, biconvex, round, film coated tablet with “BMS” debossed on one side and “524” on the other side

SPRYCEL 100 mg tablet is white to off-white, biconvex, oval, film coated tablet with “BMS 100” debossed on one side and “852” on the other side

SPRYCEL film coated tablets, 20 mg, 50 mg and 70 mg, are supplied in HDPE bottles containing 60 tablets.

SPRYCEL film coated tablets, 100 mg, are supplied in HDPE bottles containing 30 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

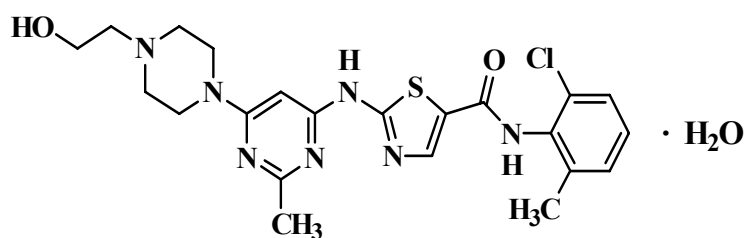
#### Drug Substance

Proper name: dasatinib

Chemical name: *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

Molecular formula:  $C_{22}H_{26}ClN_7O_2S \cdot H_2O$

Structural formula:



Molecular weight: 488.01 (anhydrous free base)

Physicochemical properties: Dasatinib is a white to off-white powder, which may contain lumps, and has a melting point of 280°–286° C. The drug substance is insoluble in water (0.008 mg/mL) at 24 ± 4° C. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pK<sub>a</sub>) were determined to be 6.8 and 3.1, and one weakly-acidic pK<sub>a</sub> was determined to be 10.9. The solubilities of dasatinib in various solvents at 24 ± 4°C are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil.

### CLINICAL TRIALS

#### Phase II Single-Arm Studies

Four single-arm Phase II multicenter studies were conducted to determine the efficacy and safety of SPRYCEL in patients with CML or Ph+ ALL resistant to or intolerant of treatment with imatinib. The primary endpoint for the trials in chronic phase CML was Major Cytogenetic

Response (MCyR) and the primary endpoint for the trials in advanced phase CML/Ph+ ALL was major Hematological Response (MaHR).

Resistance to imatinib in the chronic phase CML patients was defined as 1) a rising white blood cell count after initiation of imatinib treatment, 2) a failure to achieve a complete hematologic response (CHR) after 3 to 6 months of imatinib therapy, 3) a loss of CHR at any point during imatinib therapy, 4) a failure to achieve a cytogenetic response after 6 months of imatinib therapy, 5) a failure to achieve a major cytogenetic response (MCyR) after 12 months of therapy, or 6) a loss of MCyR at any point during imatinib therapy. Patients were considered intolerant of imatinib if they had experienced an imatinib-related CTC Grade 3 or greater non-hematologic toxicity or any imatinib-related CTC Grade 4 hematologic toxicity lasting more than 7 days.

Progression in the chronic phase CML was defined as 1) development of accelerated or blast phase CML, 2) loss of complete hematologic or major cytogenetic response, or 3) rising WBC (doubling from nadir to  $> 20,000/\text{mm}^3$  or an increase by  $50,000/\text{mm}^3$  on 2 occasions at least 2 weeks apart in patients who achieved a complete hematological response

Resistance to imatinib in the advanced CML and Ph+ALL patients was defined as lack of hematologic response or loss of hematologic response during imatinib therapy or progression from chronic to accelerated phase or from chronic or accelerated phase to blast phase. Patients were considered imatinib-intolerant if they required either a dose reduction of imatinib to  $<400$  mg/day or discontinuation of imatinib due to drug-related toxicity.

Progression in the advanced phase CML and Ph+ALL was defined as 1) loss of a major or minor hematological response, 2) lack of a decrease in percent blasts over a 4-week period, or 3) progression from accelerated to blast phase CML

Screening for BCR-ABL mutations was not required for enrollment. Mutation analysis was performed, but was not used to make eligibility or treatment decisions. Across all Phase II studies, 47% of patients were women, 85% were white, 12% were black or asian, 22% were over the age of 65 years and 4% were over the age of 75 years. No other therapy for CML was permitted during the study with the exception of Anagrelide hydrochloride for the treatment of elevated platelet counts ( $> 700,000/\text{mm}^3$ ), and hydroxyurea for white blood cell (WBC) counts  $>50,000/\text{mm}^3$ , colony-stimulating factors, and erythropoietin. Hydroxyurea use was limited to approximately 2-week duration while the patient was on-study. Hematologic and cytogenetic response rates for the single-arm Phase II studies are reported in Table 8.

Table 7 Duration of Treatment with SPRYCEL in the single-arm and a randomized Phase II CML Studies

<b>Population</b>	<b>n</b>	<b>Median months (range)</b>	<b>≤3 m N (%)</b>	<b>&gt;3-6 m N (%)</b>	<b>≥6-12 m N (%)</b>	<b>≥12-24 m N (%)</b>	<b>&gt; 24 m N (%)</b>
<b>Chronic Phase CML</b>	488	24 (<1-31)	45 (9)	31 (6)	57 (12)	113 (23)	242 (50)
<b>Accelerated phase CML</b>	174	13 (<1-29))	27 (16)	19 (11)	39 (22)	35 (20)	54 (31)
<b>Myeloid Blast CML</b>	109	4 (<1-29)	41 (38)	23 (21)	18 (17)	14 (13)	13 (12)
<b>Lymphoid Blast CML</b>	48	3 (<1-28)	25 (52)	13 (27)	7 (15)	2 (4)	1 (2)
<b>Combined</b>	819	17 (<1-31)	138 (17)	86 (11)	121 (15)	164 (20)	310 (38)

Although the 70 mg BID dose used in these Phase II trials is not the recommended starting dose in CML and Ph+ALL, the data from these trials are provided for context with the phase III dose optimization trials. (see DOSAGE AND ADMINISTRATION for recommended starting dose)

*Chronic Phase CML, Resistant or Intolerant to Imatinib*

In the single-arm Phase II study, 387 patients were analyzed (288 resistant and 99 intolerant to prior imatinib treatment). Fifty-five percent of the patients had been treated with imatinib at doses >600 mg. In addition to imatinib, 35% of patients had received prior cytotoxic chemotherapy, 65% had received prior interferon, and 10% had received a prior stem cell transplant. Thirty-eight percent of patients had baseline mutations known to confer imatinib resistance. The median duration of treatment was 24 months. (See Tables 7 and 8.)

**Advanced Disease CML and Ph+ALL Resistant or Intolerant to Imatinib**

Three open-label, multicenter, Phase II studies were conducted with SPRYCEL: 1) in accelerated phase CML, 2) in myeloid blast CML, and 3) in lymphoid blast CML.

*Accelerated Phase CML, Resistant or Intolerant to Imatinib*

A total of 174 patients were analyzed (161 resistant and 13 intolerant to prior imatinib treatment). Fifty-two percent of the patients had been treated with imatinib at doses >600 mg. In addition to imatinib, 59% of patients had received prior cytotoxic chemotherapy, 72% had received prior interferon, and 13% had undergone a prior stem cell transplant. Fifty-two percent of patients had

baseline mutations known to confer imatinib resistance. The median duration of treatment was 13 months. (See Tables 7 and 8.)

*Myeloid Blast Phase CML, Resistant or Intolerant to Imatinib*

A total of 109 patients were analyzed (99 resistant and 10 intolerant to prior imatinib treatment). Fifty percent of the patients had been treated with imatinib at doses >600 mg. In addition to imatinib, 61% of patients had received prior cytotoxic chemotherapy, 49% had received prior interferon, and 14% had undergone a prior stem cell transplant. Thirty-nine percent of patients had baseline mutations known to confer imatinib resistance. The median duration of treatment was 3.5 months. (See Tables 7 and 8.)

*Lymphoid Blast Phase CML, Resistant or Intolerant to Imatinib*

A total of 48 patients with lymphoid blast CML were analyzed (42 resistant and 6 intolerant to prior imatinib treatment). Fifty-two percent of the patients had been treated with imatinib at doses >600 mg. In addition to imatinib, 77% of patients had received prior cytotoxic chemotherapy, 48% had received prior interferon, and 31% had undergone a prior stem cell transplant. Sixty percent of patients had baseline mutations known to confer imatinib resistance. The median duration of treatment was 3 months. (See Tables 7 and 8.)

*Ph+ ALL, Resistant or Intolerant to Imatinib*

A total of 46 patients with Ph+ ALL were analyzed (44 resistant and 2 intolerant to prior imatinib treatment). Forty-six percent of the patients had been treated with imatinib at doses >600 mg. In addition to imatinib, 91% of patients had received prior cytotoxic chemotherapy, 9% had received prior interferon, and 37% had undergone a prior stem cell transplant. Sixty-seven percent of patients had baseline mutations known to confer imatinib resistance. The median duration of treatment was 3 months. (See Table 8.)

**Table 8: Efficacy of SPRYCEL in Phase II Single-Arm Clinical Trials\***

	<b>Chronic (N = 387)</b>	<b>Accelerated (N = 174)</b>	<b>Myeloid Blast (N =109)</b>	<b>Lymphoid Blast (N = 48)</b>	<b>Ph+ ALL (N=46)</b>
<b>Hematologic Response<sup>a</sup> (%) (95% CI)</b>					
Major Hematologic Response (MaHR)	Not Applicable	<b>64 (57-72)</b>	<b>33 (24-43)</b>	<b>35 (22-51)</b>	<b>41 (27-57)</b>
Complete Hematologic Response (CHR)**	91 (88-94)	50 (42-58)	26 (18-35)	29 (17-44)	35 (21-50)
No Evidence of Leukemia (NEL)	Not Applicable	14 (10-21)	7 (3-14)	6 (1-17)	7 (1-18)
<b>Duration of Hematologic Response<sup>b</sup> (%) (Kaplan-Meier Estimates)</b>					
1 Year	92 (57-67)	79 (71-87)	71 (55-87)	29 (3-56)	32 (8-56)
2 Years	83 (78-87)	60 (50-70)	41 (21-60)	10 (0-28)	24 (2-47)
Median Duration of CHR/MaHR (months)	Median still not achieved	Median still not achieved	22.4 (14.3 - .)	4.9 (3.3-15.0)	7.6 (4.8-14.5)
<b>Cytogenetic Response<sup>c</sup> (%)***</b>					
Major Cytogenetic Response (MCyR) (95% CI)	<b>62 (57-67)</b>	40 (33-48)	34 (25-44)	52 (37-67)	57 (41-71)
MCyR based on ≥ 20 metaphases	59	36	23	44	48
Median Duration of MCyR (months)	Median still not achieved	Median still not achieved	16.8 (7.4 - .)	4.1 (1.9 - 7.9)	6.3 (3.8-11.1)
Complete Cytogenetic Response (CCyR)	54 (48-59)	33 (26-41)	27 (19-36)	46 (31-61)	54 (39-69)
CCyR based on ≥ 20 metaphases	50	29	18	38	46

\* 70 mg BID dose is not the recommended starting dose. Data are provided for context with the phase III dose optimization trials.

<sup>a</sup> **Hematologic response criteria (all responses confirmed after 4 weeks):**

Major hematologic response: (MaHR) = CHR + NEL

CHR (chronic CML): WBC ≤ institutional ULN, platelets < 450,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥ 1000/mm<sup>3</sup>, platelets ≥ 100,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

NEL (no evidence of leukemia): same criteria as for CHR but ANC ≥ 500/mm<sup>3</sup> and <1000/mm<sup>3</sup>, and/or platelets ≥ 20,000/mm<sup>3</sup> and ≤ 100,000/mm<sup>3</sup>.

<sup>b</sup> **Duration of CHR for chronic phase CML; duration of MaHR for advanced phase CML and Ph+ALL**

<sup>c</sup> **Cytogenetic response criteria:** complete (0% Ph+ metaphases) or partial (>0 %-35%). MCyR (0%-35%) combines both complete and partial responses. No response confirmation was required

\*\* A total of 223 out of 387 patients with Chronic Phase CML (58%) had abnormal blood count at entry. Two hundred and three of those patients (91%) achieved a complete hematologic response from abnormal baseline (high WBC counts becoming normal and maintained for at least 4 weeks without any concomitant therapy).

\*\*\* Not all of the patients had abnormal cytogenetics at study entry:

- A total of 346 out of 387 patients with Chronic Phase CML (89%) had abnormal cytogenetics at study entry
- A total of 167 out of 174 patients with Accelerated Phase CML (96%) had abnormal cytogenetics at study entry
- A total of 104 out of 109 patients with Myeloid Blast CML (95%) had abnormal cytogenetics at study entry
- A total of 39 out of 48 patients with Lymphoid Blast CML (81%) had abnormal cytogenetics at study entry
- A total of 32 out of 46 patients with Ph+ALL (70%) had abnormal cytogenetics at study entry

Hematologic response criteria for the advanced stages CML (accelerated phase and blast crisis) included a concept of “major hematologic response.” This group combined CHR and NEL under a single general category. This change was introduced to highlight the observation that patients achieving NEL have a durability of response similar to CHR but may have some degree of neutropenia or thrombocytopenia due to a long history of previous treatments for CML and thus do not meet the full criteria of CHR.

Based on the Kaplan-Meier estimates (which are descriptive in nature as they are derived from non-randomized single arm trials), the proportion of patients who had progression-free survival (PFS) at 2 years was 80% (95% CI: [75%-84%]) for chronic phase CML, 46% (95% CI: 38%-54%) for accelerated phase CML, 20% (95% CI: 11%-29%) for myeloid blast phase CML, 5% (95% CI: 0%-13%) for lymphoid blast phase CML, and 12% (95% CI: 2%-23%) for Ph+ALL. The estimated rate of overall survival at 2 years was 94% (95% CI: 91%-97%) for chronic phase CML, 72% (95% CI: 64%-79%) for accelerated phase CML, 38% (95% CI: 27%-50%) for myeloid blast phase CML, 26% (95% CI: 10%-42%) for lymphoid blast phase CML, and 31% (95% CI: 16%-47%) for Ph+ALL.

## Randomized Studies

*Phase II non-comparative study of SPRYCEL 70 mg twice daily or imatinib 800 mg daily:*

In the non-comparative study, chronic phase CML patients who were resistant to imatinib  $\leq 600$  mg per day were randomized in a 2:1 ratio to either SPRYCEL 70 mg BID or imatinib 800 mg daily. No imatinib-intolerant patients were enrolled. Although the 70 mg BID dose used in the Phase II trials is not the recommended starting dose in Chronic Phase CML, the data from these trials are provided for context with the phase III dose optimization trials (see DOSAGE AND ADMINISTRATION for recommended starting dose). The primary endpoint was the rate of MCyR at 12 weeks. A secondary endpoint was the duration of MCyR. Progression-free survival (PFS) was also assessed. Crossover to the alternate therapy was permitted in the event of disease progression or intolerable toxicity. In case of unsatisfactory response, the trial design allowed dose escalation for patients in the SPRYCEL arm whereas patients in the imatinib arm were to be crossed over to SPRYCEL treatment. Median duration of treatment prior to crossover was 23 months for SPRYCEL and 3 months for imatinib.

A total of 150 patients were randomized to receive treatment: 101 to SPRYCEL and 49 to imatinib. Prior to crossover, 93% of the SPRYCEL-treated patients and 82% of the imatinib-treated patients achieved a CHR. At 12 weeks (based on  $\geq 20$  metaphases counted), MCyR was achieved in 31% of the SPRYCEL-treated patients (CCyR in 18%) and 22% of the imatinib-treated patients (CCyR in 4%). Overall, a CCyR was achieved in 44% of the

SPRYCEL-treated patients and 16% of the imatinib-treated patients prior to crossover. Crossover to alternate therapy occurred in 20 patients of the SPRYCEL arm and 39 patients of the imatinib arm.

Progression was defined as any of the following events: development of accelerated or blast phase CML, loss of CHR or MCyR, increase in WBC, or death from any cause.

Based on the Kaplan-Meier estimates, the proportion of patients on dasatinib who maintained MCyR for 1 year and 18 months was 92% (95% CI:[85%-100%]) and 90% (95% CI: [82%-98%]), respectively; CCyR - 97%, 95% CI:[92%-100%]) and 94%, 95% CI: [87%-100%]), respectively; the proportion of patients on dasatinib who had progression-free survival (PFS) for 1 year and 2 years was 91% (95% CI: [85%-97%]) and 86% (95% CI: [78%- 93%]), respectively.

Based on the Kaplan-Meier estimates, the proportion of patients on imatinib who maintained MCyR for 1 year and 18 months was 74% (95% CI:[49%-100%]) and 74% (95% CI: [49%-100%]), respectively; CCyR - 100% of imatinib patients for 18 months; the proportion of patients on imatinib who had PFS for 1 year and 2 years was 73% (95% CI: [54%-91%]) and 65% (95% CI: [43%-87%]), respectively.

*Phase III dose-optimization study in chronic phase CML:* A randomized, open-label study was conducted in patients with chronic phase CML to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary endpoint was MCyR in imatinib-resistant patients. The main secondary endpoint was MCyR by total daily dose level in the imatinib-resistant patients. Other secondary endpoints included duration of MCyR and overall survival. A total of 670 patients, of whom 497 were imatinib resistant, were randomized to the SPRYCEL 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. Median duration of treatment was 22 months.

Resistance to imatinib was defined as failure to achieve a CHR (after 3 months), MCyR (after 6 months), or CCyR (after 12 months); or loss of a previous molecular response (with concurrent  $\geq 10\%$  increase in Ph+ metaphases), cytogenetic response, or hematologic response.

Progression in the chronic phase CML was defined as any of the following events: loss of a CHR or MCyR; no CHR with an increase in white blood cell count; development of accelerated or blast phase CML; a  $\geq 30\%$  increase in the number of Ph+ metaphases; or death.

Results described below are based on a minimum of 24 months follow-up.

Efficacy was achieved across all SPRYCEL treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint in imatinib resistant patients (difference in MCyR 1.9%; 95% confidence interval [-6.8%–10.6%]). The main secondary endpoint of the study also showed comparable efficacy (non-inferiority) among imatinib-resistant patients between the 100 mg total daily dose and the 140 mg total daily dose (difference in MCyR -0.2%; 95% CI [-8.9%–8.5%]). Efficacy results are presented in Table 9.

**Table 9: Efficacy of SPRYCEL in Phase III Dose-Optimization Study: Chronic Phase CML**

	100 mg once daily n = 167	50 mg twice daily <sup>a</sup> n = 168	140 mg once daily <sup>a</sup> n = 167	70 mg twice daily <sup>a</sup> n = 168
<b>All Patients</b>				
<b>Imatinib-Resistant Patients</b>	n = 124	n = 124	n = 123	n = 126
<b>Haematologic Response Rate<sup>b</sup> (%) (95% CI)</b>				
CHR	<b>92% (86-95)</b>	92% (87-96)	87% (81-92)	88% (82-93)
<b>Cytogenetic Response<sup>c</sup> (%) (95% CI)</b>				
<b>MCyR</b>				
All Patients	<b>63% (56-71)</b>	61% (54-69)	63% (55-70)	61% (54-69)
Imatinib-Resistant Patients	<b>59% (50-68)</b>	56% (47-65)	58% (49-67)	57% (48-66)
<b>CCyR</b>				
All Patients	<b>50% (42-58)</b>	50% (42-58)	50% (42-58)	54% (46-61)
Imatinib-Resistant Patients	<b>44% (35-53)</b>	42% (33-52)	42% (33-52)	48% (39-57)

<sup>a</sup> Not a recommended starting dosage of SPRYCEL for chronic phase CML

<sup>b</sup> Haematologic response criteria (all responses confirmed after 4 weeks):

CHR (chronic CML): WBC ≤ institutional ULN, platelets < 450,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.

<sup>c</sup> Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (> 0%-35%). MCyR (0%-35%) combines both complete and partial responses.

A total of 378 out of 670 patients (56%) with chronic phase CML had abnormal blood count at entry; 317 out of the 378 (84%) patients achieved a CHR from an abnormal baseline (high WBC counts becoming normal and maintained for at least 4 weeks without any other concomitant therapy). A total of 554 out of 670 patients (83%) had abnormal cytogenetics at study entry.

Major molecular response (defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples) was evaluated in a subset of assessed patients who had a CCyR. Major molecular response was achieved in 69% (95% CI [58-79%]) of all patients and 72% (95% CI [58-83%]) of imatinib-resistant patients in the SPRYCEL 100 mg once daily group; 70% (95% CI [59-80%]) of all patients and 69% (95% CI [54-81%]) of imatinib-resistant patients in the SPRYCEL 50 mg twice daily group; 72% (95% CI [60-82%]) of all patients and 63% (95% CI [48-76%]) of imatinib-resistant patients in the SPRYCEL 140 mg once daily group; and 66% (95% CI [54-76%]) of all patients and 64% (95% CI [50-76%]) of imatinib-resistant patients in the SPRYCEL 70 mg twice daily group.

Based on the Kaplan-Meier estimates, the proportion of patients among those who achieved MCyR on 100 mg of SPRYCEL once daily and 70 mg twice daily, and maintained MCyR for 18 months was 93% (95% CI: [88%-98%]) and 88% (95% CI: [81%-95%]), respectively.

Based on the Kaplan-Meier estimates, the proportions of patients with PFS at 1 year were 90% (95% CI [86-95%]) of all patients and 88% (95% CI [82-94%]) of imatinib-resistant patients in the 100 mg once daily group; 86% (95% CI [81-92%]) of all patients and 84% (95% CI [77-91%]) of imatinib-resistant patients in the 50 mg twice daily group; 88% (95% CI [82-93%]) of all patients and 86% (95% CI [80-93%]) of imatinib-resistant patients in the 140 mg once daily group; and 87% (95% CI [82-93%]) of all patients and 85% (95% CI [78-91%]) of imatinib-resistant patients in the 70 mg twice daily group. At 2 years, the estimated rates of PFS were 80% (95% CI [73-87%]) of all patients and 77% (95% CI [68-85%]) of imatinib-resistant patients in the 100 mg once daily group; 76% (95% CI [68-83%]) of all patients and 73% (95%

CI [64-82%]) of imatinib-resistant patients in the 50 mg twice daily group; 75% (95% CI [67-82%]) of all patients and 68% (95% CI [59-78%]) of imatinib-resistant patients in the 140 mg once daily group; and 76% (95% CI [68-83%]) of all patients and 72% (95% CI [63-81%]) of imatinib-resistant patients in the 70 mg twice daily group.

The estimated rates of overall survival at 1 year were 96% (95% CI [93-99%]) of all patients and 94% (95% CI [90-98%]) of imatinib-resistant patients in the 100 mg once daily group; 96% (95% CI [93-99%]) of all patients and 95% (95% CI [91-99%]) of imatinib-resistant patients in the 50 mg twice daily group; 96% (95% CI [93-99%]) of all patients and 97% (95% CI [93-100%]) of imatinib-resistant patients in the 140 mg once daily group; and 94% (95% CI [90-98%]) of all patients and 92% (95% CI [87-97%]) of imatinib-resistant patients in the 70 mg twice daily group. At 2 years, the estimated rates of overall survival were 91% (95% CI [86-96%]) of all patients and 89% (95% CI [84-95%]) of imatinib-resistant patients in the 100 mg once daily group; 90% (95% CI [86-95%]) of all patients and 89% (95% CI [83-94%]) of imatinib-resistant patients in the 50 mg twice daily group; 94% (95% CI [90-97%]) of all patients and 94% (95% CI [89-98%]) of imatinib-resistant patients in the 140 mg once daily group; and 88% (95% CI [82-93%]) of all patients and 84% (95% CI [78-91%]) of imatinib-resistant patients in the 70 mg twice daily group.

Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77%, CCyR in 67%, and major molecular response in 64%. Based on the Kaplan-Meier estimates, all imatinib-intolerant patients who achieved MCyR (100%) maintained MCyR for 1 year and 92% (95% CI: [80%-100%]) among those who achieved MCyR maintained MCyR for 18 months. The estimated rate of PFS in this population was 97% (95% CI: [92%-100%]) at 1 year and 87% (95% CI: [76%-99%]) at 2 years. The estimated rate of overall survival was 100% at 1 year and 95% (95% CI: [88%-100%]) at 2 years.

*Phase III dose-optimization study in advanced phase CML and Ph+ALL:* A randomized, open-label study was conducted in patients with accelerated phase CML, myeloid blast phase CML, lymphoid blast phase CML, or Ph+ALL to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary endpoint was the rate of MaHR. Secondary endpoints included the rate of MCyR, duration of MaHR, PFS, and overall survival. A total of 611 patients were randomized to the SPRYCEL 140 mg once daily or 70 mg twice daily group. Median duration of treatment was 14 months for accelerated phase CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML, and 3 months for Ph+ALL.

Resistance to imatinib was defined as no hematologic response or a  $\geq 50\%$  increase in blasts in peripheral blood; loss of a hematologic response; progression to blast or accelerated phase CML with blasts in peripheral blood while on treatment with imatinib.

Progression was defined as follows:

- Accelerated phase CML: Loss of a CHR, NEL, or MiHR; development of blast phase CML; no decrease from baseline percent blasts in peripheral blood or bone marrow; development of extramedullary sites (other than spleen or liver); a  $\geq 50\%$  increase in blasts in peripheral blood; or death.

- Blast phase CML or Ph+ALL: Loss of a CHR, NEL, or MiHR; no decrease from baseline percent blasts in peripheral blood or bone marrow; a  $\geq 50\%$  increase in blasts in peripheral blood; or death.

Results described below are based on a minimum of 24 months follow-up.

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [-7.1% - 8.7%]). Response rates are presented in Table 10.

**Table 10: Efficacy of SPRYCEL in Phase III Dose-Optimization Study: Advanced Phase CML and Ph+ALL**

	140 mg Once Daily				70 mg Twice Daily <sup>a</sup>			
	Accelerated (n=158)	Myeloid Blast (n=75)	Lymphoid Blast (n=33)	Ph+ALL (n=40)	Accelerated (n=159)	Myeloid Blast (n=74)	Lymphoid Blast (n=28)	Ph+ALL (n=44)
<b>MaHR<sup>b</sup></b>	<b>66%</b>	<b>28%</b>	<b>42%</b>	<b>38%</b>	68%	28%	32%	32%
(95% CI)	(59-74)	(18-40)	(26-61)	(23-54)	(60-75)	(19-40)	(16-52)	(19-48)
<b>CHR<sup>b</sup></b>	<b>47%</b>	<b>17%</b>	<b>21%</b>	<b>33%</b>	52%	18%	14%	25%
(95% CI)	(40-56)	(10-28)	(9-39)	(19-49)	(44-60)	(10-28)	(4-33)	(13-40)
<b>NEL<sup>b</sup></b>	<b>19%</b>	<b>11%</b>	<b>21%</b>	<b>5%</b>	16%	11%	18%	7%
(95% CI)	(13-26)	(5-20)	(9-39)	(1-17)	(11-23)	(5-20)	(6-37)	(1-19)
<b>MCyR<sup>c</sup></b>	<b>39%</b>	<b>28%</b>	<b>52%</b>	<b>70%</b>	43%	30%	46%	52%
(95% CI)	(31-47)	(18-40)	(34-69)	(54-83)	(35-51)	(20-42)	(28-66)	(37-68)
<b>CCyR</b>	<b>32%</b>	<b>17%</b>	<b>39%</b>	<b>50%</b>	33%	23%	43%	39%
(95% CI)	(25-40)	(10-28)	(23-58)	(34-66)	(26-41)	(14-34)	(25-63)	(24-55)

<sup>a</sup> Not a recommended starting dosage of SPRYCEL for advanced phase CML and Ph+ALL.

<sup>b</sup> Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR: WBC  $\leq$  institutional ULN, ANC  $\geq 1000/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , no blasts or promyelocytes in peripheral blood, bone marrow blasts  $\leq 5\%$ ,  $< 5\%$  myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood  $< 20\%$ , and no extramedullary involvement.

NEL: same criteria as for CHR but ANC  $\geq 500/\text{mm}^3$  and  $< 1000/\text{mm}^3$ , or platelets  $\geq 20,000/\text{mm}^3$  and  $\leq 100,000/\text{mm}^3$ .

<sup>c</sup> MCyR combines both complete (0% Ph+ metaphases) and partial ( $> 0\%$ -35%) responses.

CI = confidence interval ULN = upper limit of normal range.

A total of 529 out of 611 patients (87%) with advanced phase CML or Ph+ALL had abnormal blood count at entry; 238 out of the 529 (45%) patients achieved a MaHR from an abnormal baseline (high WBC counts becoming normal and maintained for at least 4 weeks without any other concomitant therapy)

A total of 526 out of 611 patients (86%) had abnormal cytogenetics at study entry.

The median duration of MaHR in patients with accelerated phase CML was not reached for either group; the median PFS was 25 months and 26 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; and the median overall survival was not reached for

the 140 mg once daily group and 31 months for the 70 mg twice daily group. In patients with myeloid blast phase CML, the median duration of MaHR was 8 months and 9 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months for both groups; and the median overall survival was 8 months for both groups. In patients with lymphoid blast phase CML, the median duration of MaHR was 5 months and 8 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 5 months for both groups, and the median overall survival was 11 months and 9 months, respectively.

## DETAILED PHARMACOLOGY

### Nonclinical pharmacodynamics

Extensive *in vitro* and *in vivo* studies demonstrated that dasatinib is a potent inhibitor of BCR-ABL and SRC family kinases along with a number of other kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGF $\beta$  receptor. Dasatinib is active *in vitro* and *in vivo* in numerous nonclinical models of CML representing variants of both imatinib-sensitive and -resistant diseases. Nonclinical studies show that dasatinib can overcome the imatinib resistance that results from divergent mechanisms including BCR-ABL kinase domain mutations, BCR-ABL overexpression, activation of alternate signaling pathways involving the SRC family kinases, and multidrug resistance gene overexpression.

Nonclinical studies demonstrate that dasatinib is capable of binding to the active conformation of BCR-ABL kinase domains, and is predicted to bind to the inactive form. Dasatinib is 300- to 1000-fold more potent than imatinib in killing human CML cells that harbor wild-type or mutant BCR-ABL *in vitro*. In a murine model of CML, dasatinib prevents the progression of chronic CML to blast phase. *In vivo*, dasatinib inhibits the growth and prolonged the survival of mice bearing xenografts of imatinib-sensitive (including an intracranial model) and one imatinib-resistant CML cell line.

### Nonclinical pharmacokinetics

The absorption, distribution, metabolism and excretion properties of dasatinib were evaluated in a series of *in vitro* and *in vivo* studies in mice, rats, rabbits, dogs and monkeys. Dasatinib had a good intrinsic membrane permeability *in vitro* and was rapidly absorbed following oral administration in all species and humans.

In rats and monkeys, systemic exposure was dose related with no apparent gender differences. No notable accumulation was observed after once-daily repeated dosing. After oral administration of [<sup>14</sup>C] dasatinib to rats, monkeys, and humans, drug-derived radioactivity was recovered primarily in the feces (>76%), with only a small portion of the dose (<7%) excreted in the urine. In all species tested, dasatinib was shown to undergo extensive metabolism, including hydroxylation, N-oxidation, N-dealkylation, oxidation to form a carboxylic acid, glucuronidation and sulfation. Dasatinib was the most abundant drug-related component in the plasma from these species, with multiple oxidative and conjugated metabolites also present. All metabolites

identified in human plasma were also found in monkey plasma. The ADME profiles of dasatinib in mice, rats, rabbits, dogs and monkeys as compared to humans suggest that these species were appropriate for safety assessment of dasatinib and its metabolites.

Multiple enzymes were involved in the metabolism of dasatinib with CYP3A4 playing a major role. The involvement of CYP3A4 was confirmed in clinical studies where the exposure of dasatinib was substantially decreased (> 80%) when it was administered 12 hours following 7-day treatment with rifampin, a potent inducer of CYP3A4. In vitro studies indicated that dasatinib was not an inducer of CYP enzymes. It inhibited CYP2C8 in a competitive manner and CYP3A4 in a time dependent manner. Based on the C<sub>max</sub> of dasatinib at the therapeutic dose, the probability of drug-drug interactions is low with co-administered drugs that are CYP2C8 substrates. However, there is a possibility of interaction with drugs that are CYP3A4 substrates given that clinical study with co-administration of dasatinib with simvastatin resulted in a moderate increase in the exposure of simvastatin and its acid.

## **TOXICOLOGY**

### **Acute Toxicity**

The single-dose oral toxicity of dasatinib was evaluated in rats at doses of 30, 100, and 300 mg/kg, and in monkeys at doses of 15, 25, and 45 mg/kg. In rats, dasatinib at 30 mg/kg was tolerated, and doses  $\geq$  100 mg/kg caused severe toxicity and death. Morbidity and mortality were attributed to gastrointestinal lesions resulting in fluid and electrolyte loss and impairment of mucosal integrity, bone-marrow and lymphoid depletion, and multifocal myocardial necrosis and hemorrhage. In monkeys, dasatinib was tolerated at doses up to 25 mg/kg, whereas a dose of 45 mg/kg resulted in severe toxicity and mortality at Days 1 and 2. Principal drug-related toxicities occurred in the skin (hemorrhage) at doses  $\geq$  15 mg/kg, GI and lymphoid-organ systems at doses  $\geq$  25 mg/kg, and kidney at 45 mg/kg.

## Acute Toxicity

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
Rat / SD	Oral gavage	Single dose	30, 100, 300	10 M 10 F	<p><u>≥ 30 mg/kg</u>: Dose-related decreased food intake, mucous feces, soiled/rough haircoat, dehydration, chromodacryorrhea, and chromorhinorrhea. Decreased size and weight of the thymus, decreased spleen weights (M), increased liver weights (F), red discoloration, ulceration, hemorrhage, and/or edema in the stomach, bone marrow depletion, and lymphoid depletion in the thymus, spleen, and/or lymph nodes. Decreases in total leukocyte, lymphocyte, monocyte, and platelet counts; increases in fibrinogen, ALT and AST, and decreases in albumin, total protein, albumin/globulin ratio, ALP, potassium, calcium and phosphorus.</p> <p><u>≥ 100 mg/kg</u>: Mortality (55% at 100 mg/kg by Day 4, 100% at 300 mg/kg by Day 3). Prior to death, decreased activity, hunched posture, pallor, surface hypothermia, ptosis, tremors (F), and absence of feces (F). Hemorrhage and/or coagulative necrosis, macrophage infiltration, hemosiderosis, and fibrosis in the heart, Red/black discoloration of the intestines and lymph nodes, red discoloration of the ovaries, tan discoloration of the liver, and decreased size of the spleen. Enteropathy in the small intestine, hemorrhage or ulceration in the small intestine (F at 300 mg/kg), renal tubular dilatation and epithelial vacuolation, increases in urinary blood and bilirubin (M), lymphoid depletion in intestinal lymphoid nodules, single-cell necrosis in the liver (F), hemorrhage in the epididymides, and testicular degeneration.</p>
Monkey / Cynomolgus	Oral gavage	Single dose	15, 25, 45	2 M 2 F	<p><u>≥ 15 mg/kg</u>: Decreased activity, surface hypothermia with decreased body temperature, dehydration, and hemorrhages at multiple sites (thorax, limbs, gingiva, head, neck and, in 1 monkey, retina). Increases in AST, decreases in total protein, globulins, and albumin, and increases or decreases in phosphorus.</p> <p><u>≥ 25 mg/kg</u>: Fecal changes (soft, liquid, bloody), pallor of mucous membranes, and decreased body weights and food intake. Lymphoid depletion in the spleen, lymph nodes, and lymphoid nodules of the stomach and intestines, and, in 1 monkey, edema in the stomach. Increases in ALT and urea nitrogen, and decreases in calcium, cholesterol, triglycerides, and <math>\gamma</math>-GT.</p> <p><u>45 mg/kg</u>: Mortality (100% by Days 1 or 2). Prior to death, emesis and increased muscle tone and tremors. Red or abnormal contents of the intestines (F), hemorrhage in the tongue, red discoloration and hemorrhage in the stomach and intestines, dilatation of cortical tubules of the kidney (F), increases in creatinine and potassium (F).</p>

## **Short- and Long-Term Toxicity**

Repeat-dose oral toxicity studies were conducted in rats for 2 weeks to 6 months, and in monkeys for 10 days to 9 months. Repeat-dose oral toxicity studies were conducted using a daily dosing regimen (2-week and 6-month studies in rats) or a 5-days on, 2-days off dosing schedule (1-month study in rats, and 10-day, 1-month, and 9-month studies in monkeys) to support a flexible clinical development plan. In both rats and monkeys, the principal drug-related toxicities were manifested in the GI and lymphoid-organ systems. Hematopoietic (bone marrow) toxicity was also a consistent finding in rats following single or repeated oral doses of dasatinib, and was accompanied by decreases in erythrocyte, lymphocyte, and platelet counts. In monkeys, minimal bone marrow toxicity occurred only in a small number of animals following repeat dosing, and was generally accompanied by decreases in erythrocyte and lymphocyte counts. In a 9-month monkey study, toxicity related to gastroenteropathy, lymphocytic depletion and others necessitated euthanasia of 50% of the animals at exposures that were only half of the systemic exposure in humans at a dose of 70 mg BID.

## Short- and Long-Term Toxicity

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
Rat / SD	Oral gavage	2 weeks (daily dosing)	1, 15, 30	6 M  6 F	<p><u>1 mg/kg</u>: No drug-related changes.</p> <p><u>≥ 15 mg/kg</u>: Chromorrhinorrhea, soiled/rough haircoat, dehydration, soft feces, and bloated/swollen abdomen (F at 15 mg/kg). Distention of the GI tract with gas, fluid, and/or ingesta or digesta. Enteropathy of the small and large intestines, edema of the large intestine, red discoloration of the mesenteric lymph nodes, decreased size of the thymus, and lymphoid depletion of the spleen, thymus, and lymph nodes. At 15 mg/kg, changes in erythrocyte parameters (decreases in erythrocyte counts, hemoglobin, and hematocrit, and increases in reticulocyte counts, MCV, and MCH), increased liver (F) and adrenal weights, and decreased kidney (M), thymus, and spleen weights.</p> <p><u>30 mg/kg</u>: Mortality (100%). Prior to death, decreased activity, surface hypothermia, pallor, diarrhea, hunched posture, ptosis, thin appearance, decreased body weight gain (F), body weight loss (M), and decreased food intake. Red discoloration of the small intestine (M), lymphoid depletion in the spleen and thymus, and bone-marrow haematopoietic depletion.</p>
Rat / SD	Oral gavage	1 month (5-days on, 2-days off)	0.9, 15, 25	15 M  15 F	<p><u>≥ 0.9 mg/kg</u>: Decreased food consumption (M).</p> <p><u>≥ 15 mg/kg</u>: Changes in erythrocyte parameters (decreases in erythrocyte counts, hemoglobin, and hematocrit, and increases in MCV and MCH). Decreased body-weight gain (M) and spleen weights, and increases in liver weights (F). Enteropathy in the gastrointestinal track. Lymphoid depletion, edema, and/or hemorrhage in the thymus.</p> <p><u>25 mg/kg</u>: Mortality (43%) due to enteropathy/lymphoid depletion. Distention and red discoloration of the gastrointestinal tract, hemorrhage in the stomach, edema in the cecum, red discoloration of the mesenteric lymph node, lymphoid depletion in the spleen, and hypocellularity in the bone marrow accompanied with hematological changes.</p>
Rat / SD	Oral gavage	6 months (daily dosing)	1.5, 4, 15/10/8	25 M  25 F	<p>The high dose of 15 mg/kg was reduced to 10 mg/kg in Week 8 and then to 8 mg/kg in Week 17 due to gastrointestinal toxicity.</p> <p><u>≥ 1.5 mg/kg/day</u>: Increased heart weights. Gastrointestinal changes of villous blunting/fusion/branching and/or epithelial hyperplasia, increased vacuolation in the adrenal cortex, increased corpora lutea in the ovary and decreased incidence of acyclic ovaries, fluid-filled uteri and decreased squamous metaplasia of endometrial glands in</p>

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
					the uterus.  <u>≥ 4 mg/kg/day</u> : The systemic exposure of dasatinib at 4 mg/kg was similar to that of humans at the therapeutic dose. Increased weights of ovaries, liver, adrenal glands, and thyroid/ parathyroid glands, and decreased weights of the pituitary gland. Fibrosis and crypt ectasia/abscesses in the cecum, and increased colloid in the thyroid.  <u>15/10/8 mg/kg</u> : Mortality (30%) at systemic exposure of dasatinib 2-4x that of humans at the therapeutic dose. In surviving animals, swollen abdomen, few or liquid feces, and fecal stained haircoat. Reversible bone marrow hypocellularity (minimal or moderate, 2 rats) or individual cell necrosis (minimal, 1 rat), changes in erythrocyte parameters (decreased erythrocyte counts, hemoglobin, and hematocrit, and increased MCV, MCH, and reticulocyte counts), and platelet parameters (increased platelet counts and decreases in platelet aggregation), increased neutrophil counts and fibrinogen, and decreased serum proteins (total protein, albumin, and globulins).
Dog / Beagle	Oral gavage	2 days	5	1 M 1 F	Dosing was discontinued after 2 days as a result of severe GI toxicity.
Monkey / Cynomolgus	Oral gavage	10 days	1, 10, 15 (5-days on, 2- days off), 25 (2-3 days), 62.5 (single dose)	1 M 1 F	<u>≥ 1 mg/kg/day</u> : Vomitus and fecal changes (soft, liquid, bloody, mucous).  <u>≥ 15 mg/kg/day</u> : Decreased food consumption, lymphoid depletion in the spleen and/or thymus, decreased spleen weights (15 mg/kg), and minimal enteropathy in the small intestine (10 and 15 mg/kg). Excretion of dasatinib in the urine increased from < 1% to up to 220-fold over the 10 day period in female monkeys.  <u>≥ 25 mg/kg/day</u> : Mortality (75%, both monkeys at 25 mg/kg and the female at 62.5 mg/kg; a male monkey was given a single dose of 62.5 mg/kg and discontinued). Prior to death, decreased activity, pale mucous membranes, hunched posture, and/or hypothermia. Red discoloration of the stomach (25 mg/kg) and small intestine (25 and 62.5 mg/kg), and red contents in the stomach and intestines (62.5 mg/kg). At 25 mg/kg, lymphoid depletion of intestinal lymphoid nodules and mesenteric lymph nodes and, at 62.5 mg/kg, edema, hemorrhage, and ulceration in the small intestine and tubular dilatation and degeneration in the kidney
Monkey / Cynomolgus	Oral gavage	1 month (5-days on, 2-days off)	1, 5, 15	4 M 4 F	<u>1 mg/kg/day</u> : No drug-related effects.  <u>≥ 5 mg/kg/day</u> : Fecal changes (liquid, nonformed, or no feces).  <u>15 mg/kg/day</u> : Vomitus, decreased body weight gain (F), and, in 1 M, hunched posture and thin, dehydrated appearance. Abnormal contents (gas and fluid) in the cecum and

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
					colon (F). Increases in ALT and decreases in albumin (M). Increases in liver weights and decreases in thymus weights (M). Splenic lymphoid depletion (M) and thymic lymphoid depletion.
Monkey / Cynomolgus	Oral gavage	9 months (5-days on, 2-days off)	1, 3/2, 10/6/4.5	6 M 6F	<p>As a result of GI toxicity, the high dose of 10 mg/kg was reduced to 6 mg/kg in Week 3 and then again to 4.5 mg/kg in Week 12; the intermediate dose of 3 mg/kg was reduced to 2 mg/kg in Week 28.</p> <p><u>≥ 1 mg/kg/day</u>: Fecal changes (discolored, liquid, mucoid, nonformed and/or decreased), and low or no food consumption. Erosion/ulceration, acute to subacute inflammation, and epithelial flattening in the large intestine, and increased mineralization in the kidney.</p> <p><u>≥ 3/2 mg/kg/day</u>: Mortality (50%) primarily due to GI toxicity. Mean systemic exposure of dasatinib in the animals at 3/2 mg/kg/day reached only half the AUC of humans at the therapeutic dose (70 mg, BID). Prior to death, vomitus, hunched posture, hypoactivity, and decreased individual body weights. Decreased erythrocyte and lymphocyte counts, hemoglobin, hematocrit, albumin, sodium, potassium, and chloride, and increased total leukocyte and neutrophil counts, fibrinogen, urea nitrogen, and creatinine. Red foci in the large intestine and/or stomach. Lymphoid depletion in the thymus and spleen, and decreases in erythroid cells of the bone marrow.</p> <p><u>10/6/4.5 mg/kg/day</u>: Mortality (100%). None of the monkeys in this dosing group completed the nine month study due to unscheduled euthanasia that resulted from toxicity. Erosion/ulceration in the stomach (1 F), enlarged, gas-distended GI tract (1 M), and red, fluid contents in the stomach and small intestine (1 M).</p>

## Genotoxicity

Dasatinib was clastogenic *in vitro* to dividing Chinese hamster ovary cells with and without metabolic activation at concentrations  $\geq 5$   $\mu\text{g/mL}$ . Dasatinib was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Test / Test System	Route of Administration	Duration of Dosing	Concentration/ Dose	N/Dose/ Sex	Findings
Bacterial Mutagenicity Screening (Spiral Ames reverse mutation) <i>S. typhimurium</i>	In vitro	48 hr	21 - 5000 $\mu\text{g/plate}$ , with and without rat S9 activation	NA	Not mutagenic.
Bacterial Mutagenicity Screening (Exploratory Ames reverse mutation) <i>S. typhimurium</i>	In vitro	48 hr	5 - 5000 $\mu\text{g/plate}$ , with and without rat S9 activation	NA	Not mutagenic.
Bacterial Mutagenicity (Reverse mutation, definitive study) <i>S. typhimurium</i> and <i>E. coli</i>	In vitro	46-50 hr	12.5 - 400 $\mu\text{g/plate}$ ( <i>S. typhimurium</i> ); 50-1600 $\mu\text{g/plate}$ ( <i>E. coli</i> ), with and without rat S9 activation	NA	Not mutagenic.
Cytogenetics Study Chinese hamster ovary cells	In vitro	4-20 hr	2.5 - 60 $\mu\text{g/mL}$ , with and without activation	NA	Genotoxic effects: Chromatid and chromosome structural aberrations at $\geq 20$ $\mu\text{g/mL}$ (4 hr -S9), 5 $\mu\text{g/mL}$ (4 hr +S9), and $\geq 5$ $\mu\text{g/mL}$ (20 hr -S9).
Oral Micronucleus Rat / SD	Oral gavage	3 days	10, 20, 40 mg/kg	5 M 5 F	Genotoxic effects: None.

## Reproductive Toxicity

Dasatinib, when administered to pregnant rats during organogenesis at doses of 2.5, 5, 10, or 20 mg/kg, induced fetal toxicity (embryoletality with associated decreases in litter size, and fetal skeletal abnormalities) at all doses, and maternal toxicity at doses  $\geq 10$  mg/kg. Maternal death occurred at 20 mg/kg. In a range-finding study in pregnant rabbits, dasatinib administered during organogenesis caused embryoletality of 13% at 6 mg/kg and 69% at 10 mg/kg. In the definitive embryo-fetal development study in rabbits, dasatinib did not cause maternal toxicity at 0.5, 2, or 6 mg/kg, whereas drug-related fetal skeletal changes occurred at all doses.

Study Type Species/Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
Embryofetal Development in Rats / SD	Oral gavage	10 days (GD 6 to 15)	2.5, 5, 10, 20	22 F	<p><u>≥2.5 mg/kg</u>: Embryo lethality (17%) and associated decreases in litter size. Fetal skeletal abnormalities.</p> <p><u>≥ 5 mg/kg</u>: Embryo lethality (77%). Fluid-filled thoracic and abdominal cavities, edema, microhepatia in fetus.</p> <p><u>≥ 10 mg/kg</u>: Embryo lethality (100%). Decreased maternal food consumption.</p> <p><u>20 mg/kg</u>: Maternal mortality (22% during Days 12 - 15 of gestation). Decreased maternal body weight gain.</p>
Range Finding Study in Rabbits / NZW	Oral gavage	13 days (GD 7 to 19)	1, 3, 6, 10	7 F	<p><u>1 and 3 mg/kg</u>: No drug-related effects.</p> <p><u>≥ 6 mg/kg</u>: Embryo lethality (13%). Decreased maternal body weight gain and/or weight loss, and decreased food consumption.</p> <p><u>10 mg/kg</u>: Embryo lethality (69%) and reduced number of litters with live fetuses at gestation day 29 (5/7).</p>
Embryo-fetal Development in Rabbits / NZW	Oral gavage	13 days (GD 7 to 19)	0.5, 2, 6	22 F	<p>No maternal toxicity. Delays in ossification of the fetal lumbar vertebrae (bifid arches) and pelvis (incompletely or unossified pubes), reduced ossification of hyoid (incompletely or unossified).</p> <p>6 mg/kg: 21% of fetus resorption among rabbits with post-implantation loss.</p>

## Safety Pharmacology

Dasatinib had no significant effects in an *in vitro* ligand binding study. In the hERG/IKr assay, dasatinib inhibited hERG currents by 6, 37, and 77% at 3, 10, and 30  $\mu\text{M}$ , respectively. The  $\text{IC}_{50}$  was 14.3  $\mu\text{M}$ . In the Purkinje fiber assay, dasatinib prolonged  $\text{APD}_{50}$  by 26% and  $\text{APD}_{90}$  by 11% at 30  $\mu\text{M}$ . Dasatinib at a single oral dose of 10 mg/kg in conscious, unrestrained monkeys ( $n = 6$ ) elicited increases in blood pressure (6-15% in systolic and 8-21% in diastolic) for approximately 2 hours. In addition, mean QTc interval increases of 16-19 msec were observed between 1.5 – 2.5 hours post dose in the dasatinib-treated cohort compared to the vehicle control. Although these QTc changes were not statistically significant from control, an association of these changes with dasatinib treatment can not be excluded.

The N-dealkylated metabolite of dasatinib, BMS-582691 at 10  $\mu\text{M}$  inhibited receptor-ligand binding to the adrenergic  $\beta_2$ , non-selective adrenergic  $\alpha_2$ , non-selective serotonin 5-HT<sub>1</sub>, serotonin 5-HT<sub>1A</sub>, norepinephrine transporter, and dopamine transporter receptors, and to the sodium channel. In the hERG/IKr assay, BMS-582691 inhibited hERG currents with a calculated  $\text{IC}_{50}$  of 5.8  $\mu\text{M}$  compared to 14.3  $\mu\text{M}$  for dasatinib. In the Purkinje fiber assay, BMS-582691 at 30  $\mu\text{M}$  prolonged  $\text{APD}_{50}$  and  $\text{APD}_{90}$  by 10% and 9%, respectively, and reduced  $V_{\text{max}}$  by 11%.

Study Type / Organ Systems Evaluated	Test System / Species/Strain	Route	Concentration/ Dose	N/Dose/ Sex	Findings
Receptor and Ion Channel Ligand Binding Study	Receptors, ion channels, and enzyme systems	<i>in vitro</i>	10 µM	--	No biologically significant effect on binding of ligands to receptors or ion-channels, or on acetylcholinesterase activity. BMS-582691 at 10 µM inhibited receptor-ligand binding to the adrenergic β <sub>2</sub> (50%), non-selective adrenergic α <sub>2</sub> (51%), non-selective serotonin 5-HT <sub>1</sub> (50%), serotonin 5-HT <sub>1A</sub> (54%), norepinephrine transporter (54%), and dopamine transporter (87%) receptors, and to the sodium channel (84%)
hERG/IKr Channel Assay / Cardiovascular	HEK293 cells transfected with human hERG cDNA	<i>in vitro</i>	3, 10, 30 µM	--	Dasatinib: IKr currents were inhibited by 6, 37, and 77% at 3, 10 and 30 µM, respectively. The calculated IC <sub>50</sub> was 14.3 µM. BMS-582691 inhibited IKr currents by 24, 72, and 95% at 3, 10 and 30 µM, respectively. The calculated IC <sub>50</sub> was 5.8 µM
Rabbit Purkinje Fiber Action Potential Assay/ Cardiovascular	Rabbit Purkinje fibers	<i>in vitro</i>	3, 10, 30 µM	--	Dasatinib: APD <sub>50</sub> and APD <sub>90</sub> were prolonged by 26% and 11%, respectively, at 30 µM. BMS-582691: APD <sub>50</sub> and APD <sub>90</sub> were prolonged by 10% and 9%, respectively, and V <sub>max</sub> was reduced by 11%.
Single-Dose Safety Pharmacology / Cardiovascular	Monkey / Cynomolgus	Oral, single dose	10 mg/kg	3 M 3 F	Drug-related increases in systolic (6-15%) and diastolic (8-21%) blood pressure for approximately 2 hours and mean QTc increases of 16-19 msec between 1.5 – 2.5 hours following a single oral dose.

## **Other Toxicity Studies**

The immunosuppressive potential of dasatinib was assessed in mouse models of T-cell proliferation (mixed lymphocyte response) and nonvascularized heart transplant rejection. The effects of dasatinib on in vitro platelet function were assessed in human, monkey, and rat plasma, and the effects on in vivo bleeding time were assessed in rats. The in vitro phototoxicity potential of dasatinib was assessed in mouse fibroblasts.

The effect of dasatinib on the cardiac sarcoplasmic reticulum and mitochondrial function is unknown. The potential for apoptosis in cardiomyocytes with dasatinib treatment has not been investigated, and no studies have been conducted with dasatinib to evaluate the potential signaling mechanism regulating cardiotoxicity.

## Other Toxicity Studies

Study Type / Test System	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
Mixed Lymphocyte Response Assay/Mouse	Oral gavage	3 days	5, 20, 50	3 M	<u>5 mg/kg</u> : No effect on T-cell proliferation. <u>≥ 20 mg/kg</u> : Dose-dependent inhibition of splenic T-cell proliferation.
Cardiac Transplant Study/Mouse	Oral gavage	30 days	15, 25, 50	4-5 M	<u>15 mg/kg, twice daily (continuous daily dosing)</u> : Graft rejection not inhibited. <u>25 mg/kg, twice daily (5-days on, 2-days off schedule)</u> : Graft rejection not inhibited. <u>25 mg/kg, twice daily, (continuous daily dosing)</u> : Inhibition of graft rejection.
Platelet Function / Platelets from humans, cynomolgus monkeys, and rats	In vitro	--	0.05, 0.5, 5 µg/mL	--	<u>0.05 µg/mL</u> : No effect. <u>0.5 and 5 µg/mL</u> : Inhibition of the platelet aggregation response to ADP and collagen in human platelet-rich plasma, and inhibition of shear-induced aggregation of human platelets. <u>5 µg/mL</u> : Decreased strength of human whole blood clots (29%); no effect on time to clot formation or rate of clot formation.  In each species complete inhibition of the collagen response was observed with comparable IC50 values (µg/mL) for human (0.24 ± 0.06) and cynomolgus monkey (0.23 ± 0.06), and slightly but not significantly greater potency for rat (0.13 ± 0.01).
Bleeding Time and Platelet Function/Rat	Oral gavage or IV	Single oral dose or IV infusion	4, 8, 20 (mg/kg, oral) or 630, 1260,- 2520 (µg/kg, IV)	5-9 M	<u>Oral gavage</u> : <u>4 mg/kg</u> : No effect on mesenteric bleeding time, cuticle bleeding time, or ADP-induced platelet aggregation. <u>8 mg/kg</u> : No effect on mesenteric bleeding time. The anticipated plasma concentration was not reached for evaluating the cuticle bleeding time and platelet aggregation. <u>20 mg/kg</u> : 3-fold increase in cuticle bleeding time and inhibition of the platelet aggregation response (21 and 99%) induced by 10 µM ADP and 20 µg/mL collagen, respectively.  IV infusion: Dasatinib produced dose-dependent increases in cuticle bleeding time at all doses (mean plasma concentrations as 61, 144, 273 ng/mL respectively) and proportion of vessels with re-bleeds and off scale bleeding at the high dose. A dose-dependent reduction in platelet aggregation (37%, 99% and 100%) was also observed

Study Type / Test System	Route of Administration	Duration of Dosing	Dose (mg/kg)	N/Dose/ Sex	Findings
					at all doses.
Phototoxicity Assay/Mouse fibroblasts	In vitro	--	0.353- 120 µg/mL	--	Results indicated that dasatinib is phototoxic <i>in vitro</i> to mouse fibroblasts

## **Carcinogenicity**

The carcinogenic potential of dasatinib has not been studied.

## REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC: Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institutes of Health; 1992. US Dept of Health and Human Services, Public Health Service Publication NIH 92-2621.
3. AMA Council on Scientific Affairs. Guidelines for Handling Parenteral Antineoplastics. JAMA. 1985; 253:1590-1592.
4. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990; 47: 1033-1049.
5. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). Am J Health-Syst Pharm. 1996; 53:1669-1685.
6. NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Health and Safety, Publication number 2004-165. September, 2004.
7. O'Hare, In vitro activity of Bcr- Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res. 2005; 65:4500-5.

### PART III: CONSUMER INFORMATION

#### SPRYCEL\* (dasatinib)

This leaflet is part III of a three-part "Product Monograph" published when SPRYCEL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SPRYCEL. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

SPRYCEL (dasatinib) is used to:

- treat adults who have chronic myeloid leukemia (CML) who are no longer benefiting from other available therapies for CML, including imatinib mesylate (Gleevec®).
- treat adults who have a particular form of acute lymphoblastic leukemia (ALL) called Philadelphia chromosome positive or Ph+ ALL.

##### What it does:

Chronic myeloid leukemia or CML is one form of leukemia. In CML, myeloid white blood cells multiply in an uncontrolled manner. It may take years for CML to progress because it is a slow-growing or chronic cancer. There are three phases of CML: chronic phase, accelerated phase, and blast crisis phase. As CML progresses, patients advance through these phases.

Ph+ acute lymphoblastic leukemia or Ph+ ALL is another form of leukemia. Acute leukemias progress faster than chronic leukemias. In Ph+ ALL, lymphoblastic white blood cells multiply in an uncontrolled manner.

The active ingredient of SPRYCEL is dasatinib. Dasatinib acts by inhibiting the activity of proteins within the leukemia cells of patients with CML. These proteins are responsible for the uncontrolled growth of the leukemia cells.

##### When it should not be used:

- If you have a history of allergic reactions to dasatinib or to any other ingredients in SPRYCEL (See the "*What the important non-medicinal ingredients are*" section of this leaflet for a complete list of ingredients in SPRYCEL). Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients.

##### What the medicinal ingredient is:

The active ingredient of SPRYCEL is dasatinib.

##### What the important non-medicinal ingredients are:

Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

##### What dosage forms it comes in:

SPRYCEL (dasatinib) is available in film coated tablets for oral administration in strengths 20, 50, 70 and 100 mg dasatinib (as monohydrate).

#### WARNINGS AND PRECAUTIONS

##### Serious Warnings and Precautions:

SPRYCEL should be given under the supervision of a doctor experienced in the use of anti-cancer drugs. Serious and common side effects with SPRYCEL include:

- Myelosuppression (decrease of production of blood cells),
- Bleeding which may result in death,
- Fluid retention,
- Congestive heart failure (shortness of breath, swelling, weight gain) accompanied in most if not all cases by fluid retention and pulmonary edema (fluid in the lung).

BEFORE you use SPRYCEL talk to your doctor or pharmacist if you:

- **are pregnant or planning to become pregnant.** SPRYCEL may harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while undergoing treatment with SPRYCEL.
- **are breast-feeding.** It is not known if SPRYCEL can pass into your breast milk or if it can harm your baby. Do not breast-feed if you are taking SPRYCEL.
- **are a sexually active male.** Men who take SPRYCEL are advised to use a condom to avoid pregnancy in their partner.
- **have a liver problem.**
- **Have a heart problem,** such as arrhythmia, long QT syndrome (a hereditary disorder of the heart electrical rhythm).
- are lactose intolerant or have been diagnosed with an intolerance to some sugars.
- are taking medicines to thin the blood or prevent clots. SPRYCEL may cause bleeding

Talk to you doctor or pharmacist if you have:

- muscle aches/pains or weakness, or dark-colored urine

## INTERACTIONS WITH THIS MEDICATION

SPRYCEL may interact with other drugs, including those you take without a prescription. You must tell your doctor or pharmacist about all drugs, including prescription and non-prescription drugs, herbal products (e.g. St. John's Wort) and supplements you are taking or planning to take before you take SPRYCEL.

- Examples of medicines that increase the level of SPRYCEL in your bloodstream include ketoconazole, SPORANOX® (itraconazole), erythromycin, BIAXIN® (clarithromycin).
- Examples of medicines that decrease the amount of SPRYCEL in your bloodstream include dexamethasone, phenytoin, carbamazepine, rifampicin, and phenobarbital.
- Examples of a medicine whose blood levels might be altered by SPRYCEL include SANDIMMUNE®/NEORAL® (cyclosporine), simvastatin.

The absorption of SPRYCEL from your stomach into your bloodstream is best accomplished in the presence of stomach acid. You should avoid taking medicines that reduce stomach acid such as cimetidine, famotidine, ranitidine, or omeprazole while taking SPRYCEL. Medicines that neutralize stomach acid, such as aluminium hydroxide/magnesium hydroxide, calcium carbonate or calcium carbonate and magnesia may be taken up to 2 hours before or 2 hours after SPRYCEL.

Since SPRYCEL therapy may be associated with bleeding events, tell your doctor if you are regularly using blood thinners, including medications such as warfarin sodium or aspirin.

## PROPER USE OF THIS MEDICATION

### Usual dose:

The usual dose for chronic phase CML is 100 mg once a day, either in the morning or in the evening.

The usual dose for accelerated or blast crisis CML or Ph+ALL is 140 mg once daily, either in the morning or in the evening.

The tablets should be swallowed whole, not crushed. They can be taken with or without food. Try to take SPRYCEL at the same time each day.

Avoid taking grape fruit juice since it may increase the blood levels of SPRYCEL.

### Overdose:

If you think you may have taken more SPRYCEL than you should, talk to your doctor immediately.

### Missed Dose

If you miss a dose of SPRYCEL, take your next scheduled dose at its regular time. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients taking SPRYCEL will experience some mild to moderate side effects. Most side effects can be managed by your doctor through additional medications, dose adjustments, or other measures.

The following information describes the most important side effects of which you must be aware. It is not a comprehensive list of all side effects recorded in clinical trials with SPRYCEL. You should report any unusual symptoms to your doctor.

Common side effects of SPRYCEL therapy include diarrhea, fever, headache, fatigue, nausea, skin rash, shortness of breath, cough, vomiting, pain, stomach pain, infection, upper respiratory tract infection, muscle aches, joint aches, and bone and extremity pain.

Other important common side effects include:

- **Low Blood Counts:** As with many leukemia drugs, therapy with SPRYCEL can be associated with low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your doctor will monitor your blood counts frequently after you start SPRYCEL, and may adjust your dose of SPRYCEL or withhold the drug temporarily in the event your blood counts drop too low, or administer additional supportive medicines to help your body regain normal blood levels. In the most severe cases, you may need to receive transfusions of red blood cells or platelets. If you develop a fever while your blood counts are depressed, you should notify your doctor immediately.
- **Bleeding:** Therapy with SPRYCEL may be associated with bleeding from a variety of sources. The most serious bleeding events observed in clinical studies included bleeding from the gastrointestinal tract and, bleeding into the brain. Bleeding into the brain resulted in the death of nine patients (less than 1% of all patients in clinical trials). The serious bleeding events were associated with very low platelet counts. Less severe bleeding events included bleeding from the nose, the gums, bruising of the skin and excessive menstrual bleeding. Your doctor will monitor your blood counts regularly, but you should notify your physician

immediately should you experience bleeding or easy bruising, no matter how mild.

- **Fluid Retention:** Therapy with SPRYCEL may be associated with fluid building up under the skin of your lower extremities and around your eyes. In more severe cases, fluid may accumulate in the lining of your lungs, the sac around your heart, or your abdominal cavity. If you experience swelling, weight gain, or increasing shortness of breath it could be the result of fluid retention and you should report these events immediately to your doctor. Your doctor can manage fluid retention in a variety of ways while you are receiving SPRYCEL.
- **Heart Rhythm Change:** SPRYCEL has the potential to induce changes in heart rhythm in susceptible individuals who have certain inherited cardiac syndromes, take medication to control heart rhythm, or are prone to low levels of potassium or magnesium in their blood. Your doctor can assess your risk by reviewing the complete list of medications that you are taking and by checking your blood and electrocardiogram.

Other important uncommon side effects include:

- **Liver toxicity:** Liver problems such as liver inflammation and increased liver enzyme levels

Based on ongoing monitoring after the approval of SPRYCEL, the following events have been reported: inflammation of the lungs, blood clots in the blood vessels, irregular heart rhythm, and deaths from gastrointestinal bleeding. These events may or may not have been related to SPRYCEL

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Bleeding or bruising without having an injury no matter how mild, blood in vomit, stools or urine, or black stools		✓	
Common	Fever, severe chills (these can be signs of infections)		✓	
Common	Swelling, weight gain, increasing shortness of breath (these could be signs of fluid retention)		✓	
Common	Dizziness, irregular and/or forceful heart beat, faint		✓	✓
Uncommon	Symptoms of muscle aches/pains or weakness, or dark urine		✓	
Uncommon	Yellow skin and eyes, nausea, loss of appetite, dark-coloured urine (liver damage)		✓	

*This is not a complete list of side effects. For any unexpected effects while taking SPRYCEL, contact your doctor or pharmacist.*

### HOW TO STORE IT

SPRYCEL (dasatinib) tablets should be stored at room temperature between 15°–30° C. Keep out of the reach and sight of children.

Do not use SPRYCEL after the expiry date which is stated on the label, blister or carton after EXP.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:

Canada Vigilance National Office  
Marketed Health Products Safety  
and Effectiveness Information Bureau  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Bristol-Myers Squibb Canada, at 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada.

Last revised: 12 May 2010

\* SPRYCEL is a TM of Bristol-Myers Squibb Company used under licence by Bristol-Myers Squibb Canada.

Other brands listed are the trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company.