HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL® (dasatinib) Tablet for Oral Use
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	05/2009
Dosage and Administration (2)	05/2009
Warnings and Precautions, Fluid Retention (5.3)	05/2009

----------INDICATIONS AND USAGE----------

SPRYCEL is a kinase inhibitor indicated for

- treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. (1, 14)
- treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Chronic phase CML: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL: 140 mg once daily. (2)

Administered orally, with or without a meal. Tablets should not be crushed or cut. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 20 mg, 50 mg, 70 mg, and 100 mg. (3, 16)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Myelosuppression:* Severe thrombocytopenia, neutropenia, and anemia may occur and require dose interruption or reduction. Monitor complete blood counts regularly. (2.3, 5.1, 6.1)
- *Bleeding Related Events (mostly associated with severe thrombocytopenia):* CNS hemorrhages, including fatalities, have occurred. Severe gastrointestinal hemorrhage may require treatment interruptions and transfusions. Use SPRYCEL with caution in patients requiring medications that inhibit platelet function or anticoagulants. (5.2, 6.1)
- *Fluid Retention:* SPRYCEL is associated with fluid retention, sometimes severe, including ascites, edema, and pleural and pericardial effusions. Manage with appropriate supportive care measures. (5.3, 6.1)
- *QT Prolongation:* Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.4)
- Fetal harm may occur when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.5, 8.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%) included myelosuppression, fluid retention events, diarrhea, headache, dyspnea, skin rash, fatigue, nausea, and hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- *CYP3A4 Inhibitors:* May increase dasatinib drug levels and should be avoided. If coadministration cannot be avoided, monitor closely and consider reducing SPRYCEL dose. (2.1, 7.1)
- *CYP3A4 Inducers:* May decrease dasatinib drug levels. If coadministration cannot be avoided, consider increasing SPRYCEL dose. (2.1, 7.2)
- *Antacids:* May decrease dasatinib drug levels. Avoid simultaneous administration. If needed, administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. (7.2)
- *H_2 Antagonists/Proton Pump Inhibitors:* May decrease dasatinib drug levels. Consider antacids in place of H_2 antagonists or proton pump inhibitors. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Hepatic Impairment:* Use SPRYCEL with caution in patients with hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 05/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL® (dasatinib) is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib.

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

2 DOSAGE AND ADMINISTRATION

The recommended starting dosage of SPRYCEL for chronic phase CML is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg administered orally once daily. Tablets should not be crushed or cut; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

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.

2.1 Dose Modification

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John's Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, a SPRYCEL dose increase should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity *[see Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 inhibitors: CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir,

saquinavir, telithromycin, and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible, is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered. Based on pharmacokinetic studies, a dose decrease to 20 mg daily should be considered for patients taking SPRYCEL 100 mg daily. For patients taking SPRYCEL 140 mg daily, a dose decrease to 40 mg daily should be considered. These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors. However, there are no clinical data with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either the strong CYP3A4 inhibitor must be discontinued, or SPRYCEL should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the SPRYCEL dose is increased. *[See Drug Interactions (7.1).]*

2.2 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 starting dosage.

2.3 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 1.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 100 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<50 \times 10^9$/L	1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. 3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose. 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). 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.

*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.

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, and 100-mg white to off-white, biconvex, film-coated tablets. *[See How Supplied (16.1).]*

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) 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 (2.3) and Adverse Reactions (6.1)]*. In a 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 than in patients treated with other dosing regimens.

5.2 Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. In all clinical studies, severe central nervous system (CNS) hemorrhages, including fatalities, occurred in 1% of patients receiving SPRYCEL. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia.

Patients were excluded from participation in initial SPRYCEL 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 >50,000–75,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

5.3 Fluid Retention

SPRYCEL is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in <1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require

thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. In dose-optimization studies, fluid retention events were reported less frequently with once daily dosing than with other dosing regimens.

5.4 QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In 865 patients with leukemia from five single-arm studies, the mean changes in QTcF from baseline were 4–6 msec; the upper 95% confidence intervals (CIs) for all mean changes from baseline were <7 msec. Of the 2182 patients treated with SPRYCEL in clinical studies, 14 (<1%) patients had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF >500 msec.

SPRYCEL should be administered with caution to 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 SPRYCEL administration.

5.5 Use in Pregnancy

Pregnancy Category D

SPRYCEL may cause fetal harm when administered to a pregnant woman. In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities, including skeletal malformations, were observed in rats and rabbits. There are no adequate and well-controlled studies of SPRYCEL in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SPRYCEL *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Myelosuppression *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Bleeding related events *[see Warnings and Precautions (5.2)]*.
- Fluid retention *[see Warnings and Precautions (5.3)]*.
- QT prolongation *[see Warnings and Precautions (5.4)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SPRYCEL in 2182 patients with CML or Ph+ ALL in clinical studies with a minimum of 2 years follow-up (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy was 15 months (range 0.03–36 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Drug was discontinued for adverse reactions in 15% of patients in chronic phase CML, 16% in accelerated phase CML, 15% in myeloid blast phase CML, 8% in lymphoid blast phase CML, and 8% in Ph+ ALL. In a dose-optimization study in patients with chronic phase CML, the rate of discontinuation for adverse reaction was lower in patients treated with 100 mg once daily than in patients treated with other dosing regimens (10% and 16%, respectively).

The most frequently reported adverse reactions (reported in ≥20% of patients) included myelosuppression, fluid retention events, diarrhea, headache, dyspnea, skin rash, fatigue, nausea, and hemorrhage.

The most frequently reported serious adverse reactions included pleural effusion (11%), gastrointestinal bleeding (4%), febrile neutropenia (4%), dyspnea (3%), pneumonia (3%), pyrexia (3%), diarrhea (3%), infection (2%), congestive heart failure/cardiac dysfunction (2%), pericardial effusion (1%), and CNS hemorrhage (1%).

6.1 Chronic Myeloid Leukemia (CML)

The median duration of treatment for patients with chronic phase CML who received 100 mg once daily was 24 months (range 1–33 months). The median duration of treatment for patients with advanced phase CML who received 140 mg once daily was

15 months (range 0.03–36 months) for accelerated phase CML, 3 months (range 0.03–29 months) for myeloid blast phase CML, and 3 months (range 0.1–10 months) for lymphoid blast CML.

Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of the patients with CML who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 2.

Table 2: Adverse Reactions Reported in ≥10% of Patients in SPRYCEL Clinical Studies of CML

Preferred Term	100 mg Once Daily		140 mg Once Daily					
	Chronic (n=165)		Accelerated (n=157)		Myeloid Blast (n=74)		Lymphoid Blast (n=33)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
	Percent (%) of Patients							
Fluid Retention	34	4	35	8	34	7	21	6
Superficial localized edema	18	0	18	1	14	0	3	0
Pleural effusion	18	2	21	7	20	7	21	6
Generalized edema	3	0	1	0	3	0	0	0
Pericardial effusion	2	1	3	1	0	0	0	0
Congestive heart failure/cardiac dysfunction[a]	0	0	0	0	4	0	0	0
Pulmonary edema	0	0	1	0	4	3	0	0
Headache	33	1	27	1	18	1	15	3
Diarrhea	27	2	31	3	20	5	18	0
Fatigue	24	2	19	2	20	1	9	3
Dyspnea	20	2	20	3	15	3	3	3
Musculoskeletal pain	19	2	11	0	8	1	0	0
Nausea	18	1	19	1	23	1	21	3
Skin rash[b]	17	2	15	0	16	1	21	0
Myalgia	13	0	7	1	7	1	3	0
Arthralgia	12	1	10	0	5	1	0	0

Table 2: Adverse Reactions Reported in ≥10% of Patients in SPRYCEL Clinical Studies of CML

Preferred Term	100 mg Once Daily		140 mg Once Daily					
	Chronic (n=165)		Accelerated (n=157)		Myeloid Blast (n=74)		Lymphoid Blast (n=33)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
	Percent (%) of Patients							
Infection (including bacterial, viral, fungal, and non-specified)	12	1	10	6	14	7	9	0
Abdominal pain	12	1	6	0	8	3	3	0
Hemorrhage	11	1	26	8	19	9	24	9
Gastrointestinal bleeding	2	1	8	6	9	7	9	3
CNS bleeding	0	0	1	1	0	0	3	3
Vomiting	7	1	11	1	12	0	15	0
Pyrexia	5	1	11	2	18	3	6	0
Febrile neutropenia	1	1	4	4	12	12	12	12

[a] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[b] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Table 3). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 5% of patients *[see Warnings and Precautions (5.1)]*.

Grade 3 or 4 elevations of transaminase or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML

but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in patients with CML who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 3.

Table 3: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML

	Chronic Phase CML	Advanced Phase CML		
		140 mg Once Daily		
	100 mg Once Daily (n=165)	Accelerated Phase (n=157)	Myeloid Blast Phase (n=74)	Lymphoid Blast Phase (n=33)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	36	58	77	79
Thrombocytopenia	23	63	78	85
Anemia	13	47	74	52
Biochemistry Parameters				
Hypophosphatemia	10	13	12	18
Hypokalemia	2	7	11	15
Hypocalcemia	<1	4	9	12
Elevated SGPT (ALT)	0	2	5	3
Elevated SGOT (AST)	<1	0	4	3
Elevated Bilirubin	<1	1	3	6
Elevated Creatinine	0	2	8	0

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25–<50 × 10^9/L, Grade 4 <25 × 10^9/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × 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).

6.2 Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

A total of 135 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders such

as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. The most frequently reported serious adverse reactions included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), infection (5%), pyrexia (4%), pneumonia (3%), diarrhea (3%), nausea (2%), vomiting (2%), and colitis (2%).

6.3 Additional Data From Clinical Trials

The following adverse reactions were reported in patients in the SPRYCEL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance.

Gastrointestinal Disorders: *1%–<10%* – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; *0.1%–<1%* – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis.

General Disorders and Administration Site Conditions: *1%–<10%* – asthenia, pain, chest pain, chills; *0.1%–<1%* – malaise, temperature intolerance.

Skin and Subcutaneous Tissue Disorders: *1%–<10%* – pruritus, alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); *0.1%–<1%* – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, acute febrile neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome.

Respiratory, Thoracic, and Mediastinal Disorders: *≥10%* – cough; *1%–<10%* – lung infiltration, pneumonitis, pulmonary hypertension; *0.1%–<1%* – asthma, bronchospasm; *<0.1%* – acute respiratory distress syndrome.

Nervous System Disorders: *1%–<10%* – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; *0.1%–<1%* – amnesia, tremor, syncope; *<0.1%* – convulsion, cerebrovascular accident, transient ischemic attack.

Blood and Lymphatic System Disorders: *1%–<10%* – pancytopenia; *<0.1%* – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: *1%–<10%* – muscular inflammation, muscular weakness, musculoskeletal stiffness; *0.1%–<1%* – rhabdomyolysis; *<0.1%* – tendonitis.

Investigations: *1%–<10%* – weight increased, weight decreased; *0.1%–<1%* – blood creatine phosphokinase increased.

Infections and Infestations: *1%–<10%* – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes).

Metabolism and Nutrition Disorders*: 1%–<10%* – anorexia, appetite disturbances, hyperuricemia; *<0.1%* – hypoalbuminemia.

Cardiac Disorders: *1%–<10%* – arrhythmia (including tachycardia), palpitations; *0.1%–<1%* – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), myocardial infarction; *<0.1%* – cor pulmonale, myocarditis, acute coronary syndrome.

Eye Disorders: *1%–<10%* – visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye; *0.1% –<1%* – conjunctivitis.

Vascular Disorders: *1%–<10%* – flushing, hypertension; *0.1%–<1%* – hypotension, thrombophlebitis; *<0.1%* – livedo reticularis.

Psychiatric Disorders: *1%–<10%* – insomnia, depression; *0.1%–<1%* – anxiety, affect lability, confusional state, libido decreased.

Reproductive System and Breast Disorders: *0.1%–<1%* – gynecomastia, menstruation irregular.

Injury, Poisoning, and Procedural Complications: *1%–<10%* – contusion.

Ear and Labyrinth Disorders: *1%–<10%* – tinnitus; *0.1%–<1%* – vertigo.

Hepatobiliary Disorders: *0.1%–<1%* – cholestasis, cholecystitis, hepatitis.

Renal and Urinary Disorders: *0.1%–<1%* – urinary frequency, renal failure, proteinuria.

Neoplasms Benign, Malignant, and Unspecified: *0.1%–<1%* – tumor lysis syndrome.

Immune System Disorders: *0.1%–<1%* – hypersensitivity (including erythema nodosum).

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Dasatinib Plasma Concentrations

CYP3A4 Inhibitors: 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 twice daily increased the dasatinib C_{max} and AUC by four- and five-fold, respectively. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.1)]*.

7.2 Drugs That May Decrease Dasatinib Plasma Concentrations

CYP3A4 Inducers: When a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean C_{max} and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction potential should be considered. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered *[see Dosage and Administration (2.1)]*.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. 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; however, the dasatinib C_{max} increased 26%. 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_{max} were observed. Simultaneous administration of SPRYCEL with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL.

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. 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_{max} of dasatinib by 61% and 63%, respectively. The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

7.3 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_{max} and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of SPRYCEL. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

SPRYCEL may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of SPRYCEL in pregnant women. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. 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.

In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m^2/day] and rabbit: 0.5 mg/kg/day

[6 mg/m^2/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng•hr/mL (0.3-fold the human AUC in females at a dose of 70 mg twice daily) and 44 ng•hr/mL (0.1-fold the human AUC) in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, clavicle), reduced ossification (sternum; thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia.

8.3 Nursing Mothers

It is unknown whether SPRYCEL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SPRYCEL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of SPRYCEL in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 2182 patients in clinical studies of SPRYCEL, 547 (25%) were 65 years of age and over and 105 (5%) were 75 years of age and over. No differences in efficacy were observed between older and younger patients. 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 events and dyspnea.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of dasatinib was evaluated in healthy volunteers with normal liver function and patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment. Compared to the healthy volunteers with normal hepatic function, the dose normalized pharmacokinetic parameters were decreased in the patients with hepatic impairment.

No dosage adjustment is necessary in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*. Caution is recommended when administering SPRYCEL to patients with hepatic impairment.

8.7 Renal Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired renal function. Less than 4% of dasatinib and its metabolites are excreted via the kidney.

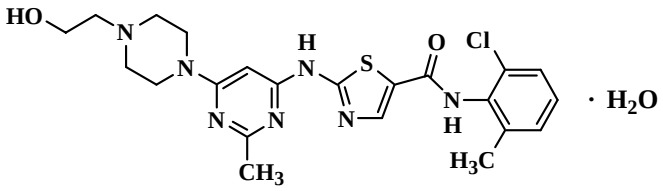
10 OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. Overdosage of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥100 mg/kg (600 mg/m^2) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥10 mg/kg (120 mg/m^2).

11 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours.

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 resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL.

Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

Dasatinib is a weak time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes.

Elimination

Elimination is primarily via the feces. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. 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.

Effects of Age and Gender

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of dasatinib.

Hepatic Impairment

Dasatinib doses of 50 mg and 20 mg were evaluated in eight patients with moderate (Child-Pugh class B) and seven patients with severe (Child-Pugh class C) hepatic impairment, respectively. Matched controls with normal hepatic function (n=15) were also evaluated and received a dasatinib dose of 70 mg. Compared to subjects with normal liver function, patients with moderate hepatic impairment had decreases in dose normalized C_{max} and AUC by 47% and 8%, respectively. Patients with severe hepatic

impairment had dose normalized C_{max} decreased by 43% and AUC decreased by 28% compared to the normal controls.

These differences in C_{max} and AUC are not clinically relevant. Dose adjustment is not necessary in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not performed with dasatinib.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

The effects of dasatinib on male and female fertility have not been studied. However, results of repeat-dose toxicity studies in multiple species indicate the potential for dasatinib to impair reproductive function and fertility. Effects evident in male animals included reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical study in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

14.1 Chronic Phase CML

Dose-Optimization Study: A randomized, open-label study was conducted in patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the study. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, 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.

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 (difference in MCyR 1.9%; 95% CI [-6.8%–10.6%]).

Efficacy results are presented in Table 4 for patients with chronic phase CML who received the recommended starting dose of 100 mg once daily. Additional efficacy results in this patient population are described after the table. Results for all patients with chronic phase CML, regardless of dosage (a starting dosage of 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily), were consistent with those for patients treated with 100 mg once daily.

Table 4: Efficacy of SPRYCEL in Chronic Phase CML

	100 mg Once Daily (n=167)
CHR[a] % (95% CI)	92% (86–95)
MCyR[b] % (95% CI)	63% (56–71)
CCyR % (95% CI)	50% (42–58)

[a] CHR (response confirmed after 4 weeks): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

In the SPRYCEL 100 mg once daily group, median time to MCyR was 2.9 months (95% CI: [2.8–3.0]). Based on the Kaplan-Meier estimates, 93% (95% CI: [88%–98%]) of patients who had achieved an MCyR maintained that response for 18 months. The estimated rate of progression-free survival and overall survival in all patients treated with 100 mg once daily was 80% (95% CI: [73%–87%]) and 91% (95% CI: [86%–96%]), respectively, at 2 years.

14.2 Advanced Phase CML and Ph+ ALL

Dose-Optimization Study: One randomized open-label study was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary efficacy endpoint was MaHR. A total of 611 patients were randomized to either the SPRYCEL 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months for both treatment groups. The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint.

The efficacy and safety of SPRYCEL were also investigated in patients with Ph+ ALL in one randomized study (starting dosage 140 mg once daily or 70 mg twice daily) and one single-arm study (starting dosage 70 mg twice daily). The primary efficacy endpoint was MaHR. A total of 130 patients were enrolled in these studies. The median duration of therapy was 3 months.

Response rates are presented in Table 5.

Table 5: Efficacy of SPRYCEL in Advanced Phase CML and Ph+ ALL

	140 mg Once Daily			
	Accelerated (n=158)	**Myeloid Blast (n=75)**	**Lymphoid Blast (n=33)**	**Ph+ ALL (n=40)**
MaHR[a] (95% CI)	66% (59–74)	28% (18–40)	42% (26–61)	38% (23–54)
CHR[a] (95% CI)	47% (40–56)	17% (10–28)	21% (9–39)	33% (19–49)
NEL[a] (95% CI)	19% (13–26)	11% (5–20)	21% (9–39)	5% (1–17)
MCyR[b] (95% CI)	39% (31–47)	28% (18–40)	52% (34–69)	70% (54–83)
CCyR (95% CI)	32% (25–40)	17% (10–28)	39% (23–58)	50% (34–66)

[a] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, 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: same criteria as for CHR but ANC ≥500/mm^3 and <1000/mm^3, or platelets ≥20,000/mm^3 and ≤100,000/mm^3.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

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

In the SPRYCEL 140 mg once daily group, the median time to MaHR was 1.9 months for patients with accelerated phase CML, 1.9 months for patients with myeloid blast phase CML, and 1.8 months for patients with lymphoid blast phase CML.

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. 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. In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once daily, the median duration of MaHR was 4.6 months. The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once daily and 70 mg twice daily were 4.0 months and 3.5 months, respectively.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004–165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999, http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. (2006) 63:1172–1193.

4. Polovich M, White JM, Kelleher LO (eds). 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd ed). Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 6.

Table 6: SPRYCEL Trade Presentations

NDC Number	Strength	Description	Tablets per Bottle
0003-0527-11	20 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “527” on the other side	60
0003-0528-11	50 mg	white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “528” on the other side	60
0003-0524-11	70 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “524” on the other side	60
0003-0852-22	100 mg	white to off-white, biconvex, oval, film-coated tablet with “BMS 100” debossed on one side and “852” on the other side	30

16.2 Storage

SPRYCEL® tablets should be stored at 25° C (77° F); excursions permitted between 15°–30° C (59°–86° F) [see USP Controlled Room Temperature].

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

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 inadvertently crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed or broken tablets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.10).

17.1 Bleeding

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising).

17.2 Myelosuppression

Patients should be informed of the possibility of developing low blood cell counts; they should be instructed to report immediately should fever develop, particularly in association with any suggestion of infection.

17.3 Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, or shortness of breath) and to seek medical attention if those symptoms arise.

17.4 Pregnancy

Patients should be informed that dasatinib may cause fetal harm when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. 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 *[see Warnings and Precautions (5.5)]*.

17.5 Gastrointestinal Complaints

Patients should be informed that they may experience nausea, vomiting, or diarrhea with SPRYCEL. If these symptoms are significant, they should seek medical attention.

17.6 Pain

Patients should be informed that they may experience headache or musculoskeletal pain with SPRYCEL. If these symptoms are significant, they should seek medical attention.

17.7 Fatigue

Patients should be informed that they may experience fatigue with SPRYCEL. If this symptom is significant, they should seek medical attention.

17.8 Rash

Patients should be informed that they may experience skin rash with SPRYCEL. If this symptom is significant, they should seek medical attention.

17.9 Lactose

Patients should be informed that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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17.10 FDA-Approved Patient Labeling

PATIENT INFORMATION

SPRYCEL® (dasatinib) Tablets

What is SPRYCEL?

SPRYCEL® (dasatinib) is a prescription medicine used to treat adults who have:

- chronic myeloid leukemia (CML) who are no longer benefitting from, or cannot tolerate, prior treatment including GLEEVEC® (imatinib mesylate).
- Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are no longer benefitting from, or cannot tolerate, prior treatment.

How does SPRYCEL work?

The active ingredient of SPRYCEL is dasatinib. Dasatinib reduces the activity of one or more proteins responsible for the uncontrolled growth of the leukemia cells of patients with CML or Ph+ ALL. This reduction allows the bone marrow to resume production of normal red cells, white cells, and platelets.

Who should not take SPRYCEL?

- **SPRYCEL is currently not recommended for patients who have not previously had a trial of GLEEVEC® (imatinib mesylate).**
- **Women who are pregnant or planning to become pregnant should not take SPRYCEL (see below).**

What should I tell my healthcare provider before I take SPRYCEL?

Tell your healthcare provider about all of your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** SPRYCEL may harm an unborn baby. Women should avoid becoming pregnant while undergoing treatment with

SPRYCEL. Tell your healthcare provider *immediately* if you become pregnant or plan to become pregnant while taking 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 or heart problem.

- are lactose intolerant.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, antacids, and herbal supplements.

SPRYCEL is eliminated from your body through the liver. The use of certain other medicines may alter the levels of SPRYCEL in your bloodstream. Likewise, levels of other medicines in your bloodstream can be affected by SPRYCEL. Such changes can increase the side effects, or reduce the activity of the medicines you are taking, including SPRYCEL.

- Medicines that increase the amount of SPRYCEL in your bloodstream are NIZORAL® (ketoconazole), SPORANOX® (itraconazole), NORVIR® (ritonavir), REYATAZ® (atazanavir sulfate), CRIXIVAN® (indinavir), VIRACEPT® (nelfinavir), INVIRASE® (saquinavir), KETEK® (telithromycin), E-MYCIN® (erythromycin), and BIAXIN® (clarithromycin).

- Medicines that decrease the amount of SPRYCEL in your bloodstream are DECADRON® (dexamethasone), DILANTIN® (phenytoin), TEGRETOL® (carbamazepine), RIMACTANE® (rifampin), and LUMINAL® (phenobarbital).

- Medicines whose blood levels might be altered by SPRYCEL are SANDIMMUNE® (cyclosporine), ALFENTA® (alfentanil), FENTANYL® (fentanyl), ORAP® (pimozide), RAPAMUNE® (sirolimus), PROGRAF® (tacrolimus), and ERGOMAR® (ergotamine).

SPRYCEL is best absorbed from your stomach into your bloodstream in the presence of stomach acid. You should avoid taking medicines that reduce stomach acid such as

TAGAMET® (cimetidine), PEPCID® (famotidine), ZANTAC® (ranitidine), PRILOSEC® (omeprazole), PROTONIX® (pantoprazole sodium), NEXIUM® (esomeprazole), ACIPHEX® (rabeprazole), or PREVACID® (lansoprazole) while taking SPRYCEL. Medicines that neutralize stomach acid, such as MAALOX® (aluminum hydroxide/magnesium hydroxide), TUMS® (calcium carbonate), or ROLAIDS® (calcium carbonate and magnesia) may be taken up to 2 hours before or 2 hours after SPRYCEL.

Since SPRYCEL therapy may cause bleeding, tell your healthcare provider if you are using blood thinners, such as COUMADIN® (warfarin sodium) or aspirin.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How do I take SPRYCEL?

Take SPRYCEL exactly as prescribed by your healthcare provider.

- If you have chronic phase CML, the usual dose is 100 mg (one 100-mg tablet or two 50-mg tablets) once daily, either in the morning or in the evening.
- If you have accelerated or blast crisis CML or Ph+ ALL, the usual dose is 140 mg (two 70-mg tablets) once daily, either in the morning or in the evening.
- Take SPRYCEL with or without a meal. Try to take SPRYCEL at the same time each day.
- Swallow SPRYCEL tablets whole with water. Do not break, cut, or crush the tablets.
- Do not drink grapefruit juice while taking SPRYCEL.
- **Depending on your response to treatment and any side effects that you may experience, your healthcare provider may adjust your dose of SPRYCEL upward or downward, or may temporarily discontinue SPRYCEL.**
- **You should not change your dose or stop taking SPRYCEL without first talking with your healthcare provider.**
- **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.

- **If you have accidentally taken more than the prescribed dose of SPRYCEL**, call your healthcare provider right away.

What are the possible side effects of SPRYCEL?

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

- **Low Blood Counts:** SPRYCEL may cause low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will check your blood counts regularly during treatment with SPRYCEL and may adjust your dose of SPRYCEL or withhold the drug temporarily in the event your blood counts drop too low. **Notify your healthcare provider immediately if you develop a fever while taking SPRYCEL.**

- **Bleeding:** SPRYCEL may cause bleeding. The most serious bleeding events observed in clinical studies included bleeding into the brain leading to death in fewer than 1% of patients, and bleeding from the gastrointestinal tract. Less severe events included bleeding from the nose, the gums, bruising of the skin, and excessive menstrual bleeding. **Tell your healthcare provider immediately if you have any bleeding or bruising while taking SPRYCEL.**

- **Fluid Retention:** SPRYCEL may cause fluid to accumulate in your legs 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. **Notify your healthcare provider immediately if you experience swelling, weight gain, or increasing shortness of breath while taking SPRYCEL.**

Other common side effects of SPRYCEL therapy include diarrhea, headache, shortness of breath, skin rash, fatigue, and nausea. Tell your healthcare provider if you have any side effects.

How will I know if SPRYCEL is working?

How well you respond to SPRYCEL therapy may depend on several factors, including the phase of your disease and prior treatments. General treatment goals for patients treated with SPRYCEL include a reduction in the number of leukemia cells and improvement of the blood cell counts. While you are on SPRYCEL, your healthcare provider will monitor these responses through routine blood tests.

How should I store SPRYCEL?

- Store SPRYCEL (dasatinib) Tablets at room temperature, 59° to 86° F (15° to 30° C).
- **Keep SPRYCEL and all medicines out of the reach of children and pets.**

General information about SPRYCEL: Medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about SPRYCEL. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for healthcare professionals. You can visit *www.sprycel.com* or call 1-800-332-2056.

What are the ingredients in SPRYCEL?

Active Ingredient: dasatinib

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

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Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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