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SPRYCEL™

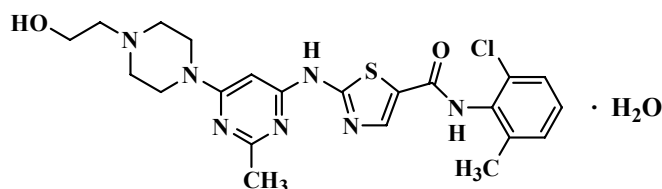
Rx only

(dasatinib) Tablets

Patient Information Included

DESCRIPTION

SPRYCEL™ (dasatinib) is an inhibitor of multiple tyrosine kinases. 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 $C_{22}H_{26}ClN_7O_2S \cdot H_2O$, 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 and has a melting point of 280°–286° C. 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.

CLINICAL PHARMACOLOGY

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

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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.

Pharmacokinetics

The pharmacokinetics of dasatinib have been evaluated in 229 healthy subjects and in 137 patients with leukemia.

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. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

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.

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Elimination

Elimination is primarily via the feces. Following a single oral dose of [¹⁴C]-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.

Special Populations

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

The pharmacokinetics of SPRYCEL have not been evaluated in pediatric patients.

Hepatic Impairment

No clinical studies were conducted with SPRYCEL in patients with impaired hepatic function. (See **PRECAUTIONS**.)

Renal Impairment

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 **PRECAUTIONS**.)

Drug-Drug Interactions

SPRYCEL is not an inducer of human CYP enzymes. SPRYCEL is a time-dependent inhibitor of CYP3A4 and may decrease the metabolic clearance of drugs that are primarily metabolized by CYP3A4. (See **PRECAUTIONS**.) At clinically relevant concentrations, dasatinib does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1.

Drugs that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors: In a study of 18 patients with solid tumors, 20-mg dasatinib QD coadministered with 200 mg of ketoconazole BID increased the dasatinib C_{max} and AUC by four- and five-fold, respectively. Substances that inhibit CYP3A4 activity (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may decrease metabolism and increase concentrations of dasatinib (see **PRECAUTIONS: Drug Interactions** and **DOSAGE AND ADMINISTRATION: Dose Modification**).

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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_{max} and AUC of dasatinib were decreased by 81% and 82%, respectively (see **PRECAUTIONS: Drug Interactions**).

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; 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. (See **PRECAUTIONS: Drug Interactions**.)

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_{max} of dasatinib by 61% and 63%, respectively. (See **PRECAUTIONS: Drug Interactions**.)

Drugs that may have their plasma concentrations 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. (See **PRECAUTIONS: Drug Interactions**.)

CLINICAL STUDIES

Four single-arm multicenter studies were conducted to determine the efficacy and safety of SPRYCEL in patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of treatment with imatinib. Resistance to imatinib included failure to achieve a complete hematologic response (within 3–6 months) or major cytogenetic response (by month 12) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance included inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity. The chronic phase CML study enrolled 186 patients, the accelerated phase CML study 107 patients, the myeloid blast phase study 74 patients, and the lymphoid blast phase CML/Ph+ ALL study 78 patients. The studies are ongoing. The results are based on a minimum of 6 months follow-up after the start of dasatinib therapy. Across all studies, 49% of patients were women, 89% were white, 10% were black or Asian, 23% were over the age of 65 years, and 3% were over the age of 75 years. Most patients had long disease histories with extensive prior treatment, including imatinib,

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cytotoxic chemotherapy, interferon, and stem cell transplant (Table 1). The maximum imatinib dose had been 400–600 mg/day in about one-half of the patients and >600 mg/day in the other half.

Table 1: Disease History Characteristics

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Median time since diagnosis in months (range)	64 (4–251)	91 (4–355)	49 (3–216)	28 (2–186)	20 (3–97)
Imatinib					
Resistant	68%	93%	92%	88%	94%
Intolerant	32%	7%	8%	12%	6%
Imatinib					
>3 years	54%	68%	47%	24%	3%
>1 year	80%	92%	85%	52%	56%
Cytotoxic chemotherapy	42%	67%	66%	79%	92%
Interferon	70%	75%	55%	48%	8%
Stem cell transplant	9%	18%	12%	33%	42%

All patients were treated with dasatinib 70 mg BID on a continuous basis. The median durations of treatment are shown in Table 2.

Table 2: Duration of Treatment with SPRYCEL

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Median duration of therapy in months (range)	5.6 (0.03–8.3)	5.5 (0.2–10.1)	3.5 (0.03–9.2)	2.8 (0.1–6.4)	3.2 (0.2–8.1)

The primary efficacy endpoint in chronic phase CML was major cytogenetic response (MCyR), defined as elimination (complete cytogenetic response, CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary endpoint in accelerated phase, myeloid blast phase, and lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response or no evidence of leukemia (defined in Table 3).

Dasatinib treatment resulted in cytogenetic and hematologic responses in patients with all phases of CML and with Ph+ ALL. The response rates for the single-arm studies are reported in Table 3. In

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chronic phase CML patients, the MCyR rate was 45% with a complete response (0% Ph+ cells) rate of 33%. The MaHR rate was 59% in accelerated phase patients, 32% in myeloid phase patients, 31% in lymphoid blast phase patients, and 42% in Ph+ ALL patients.

Most cytogenetic responses occurred after 12 weeks of treatment, when the first cytogenetic analyses were performed. Hematologic and cytogenetic responses were stable during the 6-month follow-up of patients with chronic phase, accelerated phase, and myeloid blast phase CML. The median durations of major hematologic response were 3.7 months in lymphoid blast CML and 4.8 months in Ph+ ALL.

There were no age- or gender-related response differences.

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Table 3: Efficacy in SPRYCEL Clinical Studies (All Treated Populations)^a

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Hematologic Response Rate^b (%)					
MaHR (95% CI)	n/a	59 (49–68)	32 (22–44)	31 (18–47)	42 (26–59)
CHR (95% CI)	90 (85–94)	33 (24–42)	24 (15–36)	26 (14–42)	31 (16–48)
NEL (95% CI)	n/a	26 (18–36)	8 (3–17)	5 (0.6–16)	11 (3.1–26)
Cytogenetic Response^c (%)					
MCyR (95% CI)	45 (37–52)	31 (22–41)	30 (20–42)	50 (34–66)	58 (41–74)
CCyR (95% CI)	33 (26–40)	21 (14–30)	27 (17–39)	43 (28–59)	58 (41–74)

^a Numbers in bold font are the results of primary endpoint.

^b Hematologic response criteria (all responses confirmed after 4 weeks):

Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm³, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood ≤ institutional ULN, and no extramedullary involvement.

CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥1000/mm³, platelets ≥100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood ≤ institutional ULN, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥500/mm³ and <1000/mm³, and/or platelets ≥20,000/mm³ and ≤100,000/mm³.

^c Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

n/a = not applicable.

INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates (see **CLINICAL STUDIES**). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

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

CONTRAINDICATIONS

None known.

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WARNINGS

Pregnancy (Category D)

Dasatinib 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 SPRYCEL, fetal toxicity was 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/m²/day] and rabbit: 0.5 mg/kg/day [6 mg/m²/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 the recommended dose of 70 mg BID) 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.

SPRYCEL is 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.

The potential effects of SPRYCEL on sperm counts, function, and fertility have not been studied (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility: Impairment of Fertility**). Sexually active male or female patients taking SPRYCEL should use adequate contraception.

PRECAUTIONS

General

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 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**).

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Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. Severe CNS hemorrhages, including fatalities, occurred in 1% of patients receiving SPRYCEL. Severe gastrointestinal hemorrhage occurred in 7% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 4% of patients. Most bleeding events were associated with severe thrombocytopenia.

Patients were excluded from participation in SPRYCEL (dasatinib) clinical studies if they took medications that inhibit platelet function or anticoagulants. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

SPRYCEL is associated with fluid retention, which was severe in 9% of patients, including pleural and pericardial effusion reported in 5% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in 1%. 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.

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In single-arm clinical studies in patients with leukemia treated with SPRYCEL, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 3–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <8 msec. Nine patients had QTc prolongation reported as an adverse event. Three patients (<1%) experienced a QTcF >500 msec.

SPRYCEL (dasatinib) 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.

Information for Patients (see Patient Information Leaflet)

Lactose Content

SPRYCEL contains 189 mg of lactose monohydrate in a 140-mg daily dose.

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Drug Interactions

Drugs that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin) 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 **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Drugs that may decrease dasatinib plasma concentrations

CYP3A4 Inducers: Drugs that induce CYP3A4 activity may decrease dasatinib plasma concentrations. In patients in whom CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital) are indicated, alternative agents with less enzyme induction potential should be used. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered.

St. John's wort (*Hypericum perforatum*) may decrease SPRYCEL plasma concentrations unpredictably. Patients receiving SPRYCEL should not take St. John's wort. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. 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. (See **CLINICAL PHARMACOLOGY**.)

H₂ Blockers/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H₂ blockers or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H₂ blockers or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H₂ blockers or proton pump inhibitors in patients receiving SPRYCEL therapy. (See **CLINICAL PHARMACOLOGY**.)

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: Dasatinib is a time-dependent inhibitor of CYP3A4. 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

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(ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL. (See **CLINICAL PHARMACOLOGY**.)

Hepatic Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired liver function (clinical studies have excluded patients with ALT and/or AST >2.5 times the upper limit of the normal range and/or total bilirubin >2 times the upper limit of the normal range). Metabolism of dasatinib is mainly hepatic. Caution is recommended in patients with hepatic impairment.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were not performed with dasatinib.

Mutagenesis

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.

Impairment of Fertility

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.

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Pregnancy

Pregnancy Category D (See WARNINGS)

Nursing Mothers

It is unknown whether SPRYCEL is excreted in human milk. Women who are taking SPRYCEL should not breast-feed.

Pediatric Use

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

Geriatric Use

Of the 511 patients in clinical studies of SPRYCEL (dasatinib), 119 (23%) were over 65 years of age, while 13 (3%) were over 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The data described below reflect exposure to SPRYCEL in 911 patients with leukemia from 1 Phase I and 5 Phase II clinical studies. The median duration of therapy was 6 months (range 0 - 19 months).

The majority of SPRYCEL-treated patients experienced adverse drug reactions at some time. Drug was discontinued for adverse drug reactions in 6% of patients in chronic phase CML, 5% in accelerated phase CML, 11% in myeloid blast phase CML, and 6% in lymphoid blast phase CML or Ph+ ALL.

The most frequently reported adverse events included fluid retention events such as pleural effusion; gastrointestinal events including diarrhea, nausea, abdominal pain and vomiting; and bleeding events.

The most frequently reported serious adverse events (SAEs) included pyrexia (9%), pleural effusion (8%), febrile neutropenia (7%), gastrointestinal bleeding (6%), pneumonia (6%), thrombocytopenia (5%), dyspnea (4%), anemia (3%), cardiac failure (3%), and diarrhea (2%).

All treatment-emergent adverse events (excluding laboratory abnormalities), regardless of relationship to study drug, that were reported in at least 10% of the patients in SPRYCEL clinical studies are shown in Table 4.

Table 4: Adverse Events Reported $\geq 10\%$ in Clinical Studies

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Preferred Term	All Patients (n=911)		Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
	Percent (%) of Patients					
Fluid Retention	50	9	6	6	23	9
Superficial Edema	36	1	0	2	3	2
Pleural Effusion	22	5	3	3	14	8
Other Fluid Retention	14	5	4	4	12	3
Generalized Edema	5	1	<1	0	2	1
Congestive Heart Failure/Cardiac Dysfunction ^a	4	2	3	1	5	1
Pericardial Effusion	4	1	<1	1	3	0
Pulmonary Edema	4	1	1	2	0	1
Ascites	1	1	0	1	2	2
Pulmonary Hypertension	1	0	<1	1	2	0
Diarrhea	49	5	3	10	8	6
Headache	40	2	2	2	4	6
Hemorrhage	40	10	3	18	23	17
Gastrointestinal Bleeding	14	7	2	12	14	10
CNS Bleeding	2	1	0	1	2	2
Musculoskeletal Pain	39	4	2	3	6	13
Pyrexia	39	5	1	5	13	9
Fatigue	39	3	2	4	4	8
Skin Rash ^b	35	1	1	1	1	4
Nausea	34	1	<1	0	5	2
Dyspnea	32	6	5	7	11	9
Cough	28	<1	<1	1	1	0
Infection (including bacterial, viral, fungal, non-specified)	34	7	4	8	15	13
Upper Respiratory Tract Infection/Inflammation	26	1	1	1	5	1
Abdominal Pain	25	2	1	2	4	6
Pain	26	2	<1	1	5	4
Vomiting	22	1	1	2	2	2
Anorexia	19	1	<1	2	2	3
Asthenia	19	3	1	4	6	5
Arthralgia	19	1	1	0	3	2

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Table 4: Adverse Events Reported $\geq 10\%$ in Clinical Studies

Preferred Term	All Patients (n=911)		Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
	Percent (%) of Patients					
Mucosal Inflammation (including mucositis/stomatitis)	16	1	<1	0	4	1
Dizziness	14	<1	<1	0	0	0
Weight Decreased	14	1	<1	1	1	0
Constipation	14	<1	<1	0	1	0
Chest Pain	13	1	<1	0	4	3
Neuropathy (including peripheral neuropathy)	13	1	1	1	0	0
Myalgia	12	1	0	1	2	2
Abdominal Distention	11	0	0	0	0	0
Weight Increased	11	1	<1	1	1	1
Arrhythmia	11	2	2	1	2	3
Chills	11	<1	0	1	0	0
Pruritus	11	0	0	0	0	0
Pneumonia (including bacterial, viral, and fungal)	11	6	3	8	11	10
Febrile Neutropenia	9	8	2	11	17	20

^a Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, ejection fraction decreased, and left ventricular failure.

^b Includes erythema, exfoliative rash, generalized erythema, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, systemic lupus erythematosus rash, urticaria vesiculosa, drug eruption, 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 CML or Ph+ ALL than in chronic phase CML. 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 and/or reduction; permanent discontinuation of treatment occurred in 1% of patients.

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Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia 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 CML and Ph+ ALL. Elevations in transaminases 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.

Table 5: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	49	74	83	81
Thrombocytopenia	48	83	82	83
Anemia	18	70	70	51
Biochemistry Parameters				
Hypophosphatemia	11	13	23	21
Hypocalcemia	2	9	20	15
Elevated SGPT (ALT)	1	4	7	11
Elevated SGOT (AST)	1	2	5	8
Elevated Bilirubin	<1	1	5	8
Elevated Creatinine	0	2	1	1

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 $\geq 10-50 \times 10^9/L$, Grade 4 $< 10 \times 10^9/L$); anemia (hemoglobin $\geq 65-80$ g/L, Grade 4 < 65 g/L); elevated creatinine (Grade 3 $> 3-6 \times$ upper limit 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).

Additional Data From Clinical Trials

The following treatment-emergent adverse events, regardless of relationship to study drug, were reported in patients in the SPRYCEL clinical studies at a frequency of <10%. These events are presented by frequency category. Frequent adverse events are those occurring in 1%–<10% of patients and infrequent adverse events are those occurring in 0.1%–<1% of patients. Infrequent events are included on the basis of clinical relevance.

Gastrointestinal Disorders: *Frequent* – dyspepsia, oral soft tissue disorder, gastritis, colitis, anal fissure, dysphagia; *Infrequent* – esophagitis, upper gastrointestinal ulcer, ileus, pancreatitis.

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

Skin and Subcutaneous Tissue Disorders: *Frequent* – hyperhidrosis, alopecia, dry skin, acne, urticaria, dermatitis (including eczema), photosensitivity reaction, nail disorder, pigmentation disorder; *Infrequent* – skin ulcer, acute febrile neutrophilic dermatosis, bullous conditions, palmar-plantar erythrodysesthesia syndrome.

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

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

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

Musculoskeletal and Connective Tissue Disorders: *Frequent* – muscle inflammation, muscular weakness, musculoskeletal stiffness; *Infrequent* – tendonitis, rhabdomyolysis.

Investigations: *Frequent* – blood creatine phosphokinase increased, troponin increased; *Infrequent* – platelet aggregation abnormal.

Infections and Infestations: *Frequent* – herpes virus infection, sepsis (including fatal outcomes), enterocolitis infection.

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

Cardiac Disorders: *Frequent* – palpitations, angina pectoris, cardiomegaly, myocardial infarction; *Infrequent* – pericarditis, ventricular tachycardia, acute coronary syndrome, myocarditis.

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

Vascular Disorders: *Frequent* – flushing, hypotension, hypertension; *Infrequent* – livedo reticularis.

Psychiatric Disorders: *Frequent* – insomnia, depression, anxiety, confusional state, affect lability; *Infrequent* – libido decreased.

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

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Injury, Poisoning, and Procedural Complications: *Frequent* – contusion.

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

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

Renal and Urinary Disorders: *Frequent* – urinary frequency, renal failure; *Infrequent* – proteinuria.

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

Immune System Disorders: *Infrequent* – hypersensitivity.

OVERDOSAGE

A single-dose overdose of SPRYCEL 200 mg in a patient with accelerated phase CML was reported with no associated symptoms or change in laboratory parameters. In the event of overdosage, the patient should be observed and appropriate supportive treatment given. (See **PRECAUTIONS**.)

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/m²) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥ 10 mg/kg (120 mg/m²).

DOSAGE AND ADMINISTRATION

The recommended dosage of SPRYCEL (dasatinib) is 140 mg/day administered orally in two divided doses (70 mg twice daily [BID]), one in the morning and one in the evening with or without a meal. Tablets should not be crushed or cut; they should be swallowed 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 has not been investigated.

Dose Modification

Dose increase or reduction of 20-mg increments per dose is recommended based on individual safety and tolerability.

CYP3A4 inducers such as rifampin may **decrease** SPRYCEL plasma concentrations. Coadministration of SPRYCEL with rifampin resulted in a decrease in the mean C_{max} and AUC of dasatinib by 81% and 82%, respectively (a 5-fold decrease in SPRYCEL plasma concentrations). Selection of an alternate concomitant medication with no or minimal enzyme induction potential is

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recommended. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase should be considered.

If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: Drug Interactions**). St. John's wort may decrease SPRYCEL plasma concentrations unpredictably. Patients receiving SPRYCEL should not take St. John's wort concomitantly.

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 20–40 mg daily should be considered (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: Drug Interactions**).

Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 90 mg BID (chronic phase CML) or 100 mg BID (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.

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Table 6: Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 70 mg BID)	ANC* $<0.5 \times 10^9/L$ and/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. 3. If platelets $<25 \times 10^9/L$ and/or recurrence of ANC $<0.5 \times 10^9/L$ for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 50 mg BID (second episode) or 40 mg BID (third episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg BID)	ANC $<0.5 \times 10^9/L$ and/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 50 mg BID (second episode) or 40 mg BID (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg BID.

*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.

HOW SUPPLIED

SPRYCEL™ (dasatinib) tablets are available as described in Table 7.

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Table 7: 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

Storage

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

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁹ 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.

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US Patent No 6,596,746

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PATIENT INFORMATION

SPRYCEL™ (dasatinib) TABLETS

RX ONLY

What is SPRYCEL?

SPRYCEL™ (dasatinib) is a prescription medicine used to treat adults who have chronic myeloid leukemia (CML) and to treat adults who have a particular form of acute lymphoblastic leukemia (ALL) called Philadelphia chromosome positive or Ph+ ALL. It is intended for use in patients who are no longer benefiting from treatment with the current available therapies for these diseases (resistance), including a medicine called GLEEVEC® (imatinib mesylate). It may also be used in patients who experience severe side effects from GLEEVEC and are no longer able to take it (intolerance). The long-term benefits and toxicities of SPRYCEL are currently still being studied. SPRYCEL has not been studied in children.

What is Leukemia?

Leukemia is a cancer of white blood cells, which grow in the bone marrow. In leukemia, white blood cells multiply in an uncontrolled manner, occupying the bone marrow space and spilling out into the bloodstream. As a consequence, the production of normal red blood cells (oxygen carrying cells), white blood cells (cells which fight infection), and platelets (cells which help blood clot) is compromised. Therefore, patients with leukemia are at risk of serious anemia, infections, and bleeding.

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. As CML progresses, patients advance through three phases: chronic phase, accelerated phase, and blast crisis phase. 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.

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.

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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 the fetus when given to a pregnant woman. 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.

Can I take other medicines with SPRYCEL?

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter 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).

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- Medicines that decrease the amount of SPRYCEL in your bloodstream are DECADRON[®] (dexamethasone), DILANTIN[®] (phenytoin), TEGRETOL[®] (carbamazepine), RIMACTANE[®] (rifampicin), 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[®] (aluminium hydroxide/magnesium hydroxide), TUMS[®] (calcium carbonate), or ROLAIDS[®] (calcium carbonate and magnesium) 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.

How should I take SPRYCEL?

- The usual dose is 70 mg (one 70-mg tablet) twice daily, once in the morning and once in the evening, with or without a meal. Try to take SPRYCEL at the same time each day.
- Take SPRYCEL whole. Do not break, cut, or crush the tablets.
- **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 accidentally take more than the prescribed dose of SPRYCEL, call your healthcare provider right away.**

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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 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. In some cases, you may need to receive transfusions of red blood cells or platelets. **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 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. **Notify your healthcare provider immediately if you experience bleeding or easy 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, skin rash, headache, fatigue, and nausea.

In clinical trials of over 900 patients, 7% (7 out of 100) of patients permanently stopped SPRYCEL therapy because of 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, prior treatments, or other factors your healthcare provider may discuss with you. General treatment goals for patients treated with SPRYCEL include a reduction in the number of leukemia cells and improvement or normalization of the white blood cell, red blood cell, and platelet counts.

While you are on SPRYCEL, your healthcare provider will monitor these responses through routine blood tests. The type and frequency of these tests will be determined by your healthcare provider and may vary depending on the status of your disease.

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How should I store SPRYCEL?

- Store SPRYCEL (dasatinib) Tablets at room temperature, 59° to 86° F (15° to 30 C). SPRYCEL Tablets do not require refrigeration.
- Keep the container tightly closed.
- Throw away SPRYCEL when it is outdated. Ask your pharmacist how to properly dispose of SPRYCEL.
- **Keep SPRYCEL and all medicines out of the reach of children and pets.**

General information about SPRYCEL: This medicine was prescribed for your particular condition and should be used only by you under the close supervision of your healthcare provider. The leaflet summarizes the most important information about SPRYCEL. If you would like more information, talk with your healthcare provider. If you have questions or concerns, or want more information about SPRYCEL, your healthcare provider and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your healthcare provider. Remember, no written summary can replace careful discussion with your healthcare provider.

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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