

Nonprofit PLATO Foundation Advances Oncology Education

By Caroline Helwick

Oncologists seeking continuing medical education (CME) credits at scientific meetings and online will notice a nonprofit organization among the offerings typically

predominated by the pharmaceutical industry: the PLATO Foundation (Physicians Learning And Teaching in Oncology). The PLATO Foundation is a 501(c)(3), tax-exempt organiza-

tion established in July 2010 by prIME Oncology, a global medical education company accredited by the Accreditation Council for Continuing Medical Education.

Another Avenue for CME

The PLATO Foundation was formed to advance the medical education of emerging generations of oncology and hematology practitio-

SPRYCEL® (dasatinib) Tablet for Oral Use

RX ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

SPRYCEL® (dasatinib) is indicated for the treatment of adults with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. The effectiveness of SPRYCEL is based on cytogenetic response and major molecular response rates [see Clinical Studies (14.1) in Full Prescribing Information]. The trial is ongoing and further data will be required to determine long-term outcome.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

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. In a dose-optimization study in patients with resistance or intolerance to prior imatinib therapy and 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.

Perform complete blood counts 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) in Full Prescribing Information and Adverse Reactions].

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, including fatalities, 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 per microliter. Exercise caution if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention: SPRYCEL is associated with fluid retention. In clinical trials, severe fluid retention was reported in up to 10% of patients. 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.

QT Prolongation: *In vitro* data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). Of the 2440 patients with CML treated with SPRYCEL in clinical studies, 15 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >300 ms. In 865 patients with leukemia treated with SPRYCEL in five Phase 2 single-arm studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 ms to 13.4 ms.

Administer SPRYCEL 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. Correct hypokalemia or hypomagnesemia prior to SPRYCEL administration.

Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction: Cardiac adverse reactions were reported in 5.8% of 258 patients taking SPRYCEL, including 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction. Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

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].

ADVERSE REACTIONS

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

- Myelosuppression [see Dosage and Administration (2.3) in Full Prescribing Information and Warnings and Precautions].
- Bleeding related events [see Warnings and Precautions].
- Fluid retention [see Warnings and Precautions].
- QT prolongation [see Warnings and Precautions].
- Congestive heart failure, left ventricular dysfunction, and myocardial infarction [see Warnings and Precautions].

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 clinical studies including 258 patients with newly diagnosed chronic phase CML and in 2182 patients with imatinib resistant or intolerant CML or Ph+ ALL.

In the newly diagnosed chronic phase CML trial, the median duration of therapy was 18 months; the median average daily dose was 99 mg.

In the imatinib resistant or intolerant CML or Ph+ ALL clinical trials, patients had 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). Among patients with chronic phase CML and resistance or intolerance to prior imatinib therapy, the median duration of treatment with SPRYCEL 100 mg once daily was 24 months (range 1–33 months). The median duration of treatment with SPRYCEL 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.

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. In the newly diagnosed chronic phase CML trial, drug was discontinued for adverse reactions in 6% of SPRYCEL-treated patients. Among patients with resistance or intolerance to prior imatinib therapy, the rates of discontinuation for adverse reaction were 15% 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 resistance or intolerance to prior imatinib therapy and 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 ≥10% of patients in newly diagnosed chronic phase CML included myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain, and rash. Pleural effusions were reported in 31 patients (see Table 1).

The most frequently reported adverse reactions reported in ≥20% of patients with resistance or intolerance to prior imatinib therapy included myelosuppression, fluid retention events, diarrhea, headache, dyspnea, skin rash, fatigue, nausea, and hemorrhage.

The most frequently reported serious adverse reactions in patients with newly diagnosed chronic phase CML

included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%). The most frequently reported serious adverse reactions in patients with resistance or intolerance to prior imatinib therapy 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%).

Chronic Myeloid Leukemia (CML): Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of patients are shown in Table 1 for newly diagnosed patients with chronic phase CML and Table 2 for CML patients with resistance or intolerance to prior imatinib therapy.

Table 1: Adverse Reactions Reported in ≥10% of Patients with Newly Diagnosed Chronic Phase CML

Preferred Term	All Grades		Grade 3/4	
	SPRYCEL (dasatinib) (n=258)	Imatinib (n=258)	SPRYCEL (n=258)	Imatinib (n=258)
	Percent (%) of Patients			
Fluid retention	23	43	1	1
Pleural effusion	12	0	<1	0
Superficial localized edema	10	36	0	<1
Generalized edema	3	7	0	0
Congestive heart failure/ cardiac dysfunction ^a	2	1	<1	<1
Pericardial effusion	2	<1	<1	0
Pulmonary hypertension	1	0	0	0
Pulmonary edema	<1	0	0	0
Diarrhea	18	19	<1	1
Headache	12	10	0	0
Musculoskeletal pain	12	16	0	<1
Rash ^b	11	17	0	1
Nausea	9	21	0	0
Fatigue	8	11	<1	0
Myalgia	6	12	0	0
Hemorrhage ^c	6	5	1	1
Gastrointestinal bleeding	2	<1	1	0
Other bleeding ^d	5	5	0	1
CNS bleeding	0	<1	0	<1
Vomiting	5	10	0	0
Muscle inflammation	4	19	0	<1

^a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction. ^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular. ^c Adverse reaction of special interest with <10% frequency. ^d Includes conjunctival hemorrhage, ear hemorrhage, ecchymosis, epistaxis, eye hemorrhage, gingival bleeding, hematoma, hematuria, hemoptysis, intra-abdominal hematoma, petechiae, scleral hemorrhage, uterine hemorrhage, and vaginal hemorrhage.

Table 2: Adverse Reactions Reported in ≥10% of Patients with CML Resistant or Intolerant to Prior Imatinib Therapy

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
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 (Tables 3 and 4). 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 2% of patients with newly diagnosed chronic phase CML and 5% of patients with resistance or intolerance to prior imatinib therapy [see Warnings and Precautions].

ners, as well as those in current practice. Through the award of fellowship educational grants (which will fund travel to medical conferences) and medical education programming, PLATO Foundation aims to meet the ongoing educational needs of these physicians. PLATO Found-

ation collaborates with other nonprofit organizations during major national and international hematology and oncology congresses to provide completely independent CME activities with a broad international perspective.

Jacqueline Melson, PLATO Found-

ation's fund-raising manager, said the organization was founded "to explore alternate educational opportunities" by partnering with medical institutions and other nonprofit groups. "We recognize the important contribution of the pharmaceutical industry to both clinical research and education. How-



Coming in early 2011

ever, many CME companies only work with industry. We are offering another avenue," she said.

Its first medical education activity was launched during the 33rd Annual San Antonio Breast Cancer Symposium. "Controversial Topics in Breast Cancer: Straight Talk with International Experts" was chaired by Larry Norton, MD, of Memorial Sloan-Kettering Cancer Center and Martine Piccart-Gebhart, MD, PhD, of Institute Jules Bordet, and was supported by The Breast Cancer Research Foundation and European School of Oncology.

"The symposium was quite successful. It was attended by more than 600 health-care professionals," she noted.

Using Resources 'for the Greater Good'

James O. Armitage, MD, of the University of Nebraska Medical Center, Omaha, and Editor-in-Chief of *The ASCO Post*, serves on the Board of Directors for the foundation. He commented, "Anything you can do to help train future physicians will be important to the field of oncology and to the public. We hope the PLATO Foundation will stand apart by providing activities with an unquestionable lack of bias."

Dr. Armitage acknowledged prIME Oncology for "using its resources to do something for the greater good, to provide more education for young physicians."

The website launched March 1 (www.platofoundation.org), and explains the group's mission and provides details about events. ■

Coming in future issues of The ASCO Post

Coverage of these important meetings:

2011 Genitourinary Cancers Symposium

National Comprehensive Cancer Network 16th Annual Conference

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 (dasatinib) therapy often had recovery with oral calcium supplementation. Laboratory abnormalities reported in patients with newly diagnosed chronic phase CML are shown in Table 3. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 3: CTC Grade 3/4 Laboratory Abnormalities in Patients with Newly Diagnosed Chronic Phase CML

	SPRYCEL (n=258)	Imatinib (n=258)
	Percent (%) of Patients	
Hematology Parameters		
Neutropenia	22	20
Thrombocytopenia	19	10
Anemia	11	7
Biochemistry Parameters		
Hypophosphatemia	5	24
Hypokalemia	0	2
Hypocalcemia	3	2
Elevated SGPT (ALT)	<1	1
Elevated SGOT (AST)	<1	1
Elevated Bilirubin	1	0
Elevated Creatinine	<1	1

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

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 4.

Table 4: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML: Resistance or Intolerance to Prior Imatinib Therapy

	Chronic Phase CML		Advanced Phase CML	
	100 mg Once Daily (n=165)	140 mg Once Daily	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 - $<1.0 \times 10^9/L$, Grade 4 $<0.5 \times 10^9/L$); thrombocytopenia (Grade 3 ≥ 25 - $<50 \times 10^9/L$, Grade 4 $<25 \times 10^9/L$); anemia (hemoglobin Grade 3 ≥ 65 - <80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3 - $6 \times$ upper limit of normal range (ULN), Grade 4 $>6 \times$ ULN); elevated bilirubin (Grade 3 >3 - $10 \times$ ULN, Grade 4 $>10 \times$ ULN); elevated SGOT or SGPT (Grade 3 >5 - $20 \times$ ULN, Grade 4 $>20 \times$ ULN); hypocalcemia (Grade 3 <7.0 - 6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0 - 1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0 - 2.5 mmol/L, Grade 4 <2.5 mmol/L).

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%).

Additional Data From Clinical Trials

The following adverse reactions were reported in patients in the SPRYCEL clinical studies at a frequency of 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 distention, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; 0.1%-<1% - ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis; <0.1% - protein losing gastroenteropathy. **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:** 1%-<10% - cough, 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, optic neuritis. **Blood and Lymphatic System Disorders:** 1%-<10% - pancytopenia; <0.1% - aplasia pure red cell. **Musculoskeletal and Connective Tissue Disorders:** 1%-<10% - muscular weakness; 0.1%-<1% - musculoskeletal stiffness, 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; 0.1%-<1% - sepsis (including fatal outcomes). **Metabolism and Nutrition Disorders:** 1%-<10% - anorexia, appetite disturbances; 0.1%-<1% - hyperuricemia, hypalbuminemia. **Cardiac Disorders:** 1%-<10% - arrhythmia (including tachycardia), palpitations; 0.1%-<1% - angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia); <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).

Postmarketing Experience

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

Cardiac disorders: atrial fibrillation/atrial flutter. **Vascular disorders:** thrombosis/embolism (including pulmonary embolism, deep vein thrombosis). **Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease.

DRUG INTERACTIONS

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) in Full Prescribing Information].

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) in Full Prescribing Information].

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.

H₂ Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H₂ 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. In a study of 14 healthy subjects, administration of a single 100-mg dose of SPRYCEL 22 hours following a 40-mg omeprazole dose at steady state reduced the AUC and C_{max} of dasatinib by 43% and 42%, respectively. The concomitant use of H₂ antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids (at least 2 hours prior to or 2 hours after the dose of SPRYCEL) should be considered in place of H₂ antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

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.

USE IN SPECIFIC POPULATIONS

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/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 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 microhepata.

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.

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

Geriatric Use: In the newly diagnosed chronic phase CML study, 25 patients (10%) were 65 years of age and over and 7 patients (3%) were 75 years of age and over. Of the 2182 patients in clinical studies of SPRYCEL with resistance or intolerance to imatinib therapy, 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. Compared to patients under age 65 years, patients aged 65 years and older are more likely to experience toxicity.

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) in Full Prescribing Information]. Caution is recommended when administering SPRYCEL to patients with hepatic impairment.

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.

OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. Overdose 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 and Adverse Reactions], patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

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).

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