FDA Approves New SPRYCEL® (Dasatinib) Product Labeling for Patients with Chronic-Phase CML

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- Labeling Now Includes Lower Once-Daily Starting Dose and Data from First Randomized Trial of SPRYCEL and Gleevec

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved new labeling for SPRYCEL to include a lower recommended starting dose of 100 mg once daily and safety and efficacy data in a greater number of patients with chronic-phase chronic myeloid leukemia (CML) resistant or intolerant to prior therapy including Gleevec. The product labeling now also includes data from the first randomized trial of SPRYCEL and Gleevec. SPRYCEL is indicated for the treatment of adults with chronic-, accelerated-, or myeloid or lymphoid blast-phase CML with resistance or intolerance to prior therapy including Gleevec. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

"The new, lower once-daily dose reduces the incidence of some side effects while preserving the efficacy of SPRYCEL for patients with chronic-phase CML no longer responding to currently-approved therapies," said Dr. Hagop Kantarjian, M.D., Chairman and Professor, Leukemia Department, MD Anderson Cancer Center. "Importantly, the new clinical data now included in the labeling provides further evidence to support the use of SPRYCEL to treat patients with chronic-phase CML, if their disease is no longer responding to currently available treatment including Gleevec."

The updated labeling was granted priority review and was approved in six months based primarily on two studies that enrolled chronic-phase CML patients with resistance or intolerance to Gleevec. A summary of the changes, which are detailed below, include:

-- A lower recommended starting dose of SPRYCEL 100 mg once daily based on a dose-optimization trial - the first Phase 3 trial in this patient population. This once daily dose was associated with a lower frequency of some side effects (severe myelosuppression and fluid retention).

-- Cytogenetic responses from the first randomized trial of SPRYCEL, 70 mg twice daily, and Gleevec 800 mg (400 mg twice daily), study -017. For patients receiving SPRYCEL, at 12 weeks 36 percent achieved a major cytogenetic response, the study's primary endpoint (29 percent with Gleevec), and 22 percent achieved a complete cytogenetic response (8 percent with Gleevec). With longer treatment and follow-up, 52 percent achieved a major cytogenetic response (33 percent with Gleevec), and 40 percent of patients achieved a complete cytogenetic response (16 percent with Gleevec).

The updated SPRYCEL labeling encompasses safety data for a total of 2,182 patients.

"We believe that this filing and its subsequent approval further demonstrates our commitment and dedication to patients with this disease," said Claude Nicaise, M.D., Vice President, SPRYCEL Global Development, Bristol-Myers Squibb. "Bristol-Myers Squibb is fully committed to further exploring and understanding the appropriate use of SPRYCEL through a robust clinical development program."

About the Studies

Dose-Optimization (Study -034): The Phase 3, randomized, open-label study was conducted in patients with chronic-phase CML, whose disease was resistant or intolerant to Gleevec, to evaluate the efficacy of SPRYCEL administered once daily compared with twice daily. The primary endpoint was major cytogenetic response in patients with Gleevec-resistant chronic phase CML. A total of 670 patients (498 Gleevec resistant) were randomized to 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily. Those patients who received SPRYCEL once daily achieved a comparable (non-inferior) major cytogenetic response to those who received SPRYCEL twice daily. The rate of major cytogenetic response was lower among patients aged 65 years and over. The median duration of treatment was approximately eight months. The study supports the new recommended starting dose, 100 mg once daily, for chronic-phase CML.

Incidence of selected adverse reactions (all grades) in the Phase 3 dose-optimization study in chronic-phase CML patients receiving SPRYCEL 100 mg once daily (n=165) or SPRYCEL 70 mg twice daily (n=167) included diarrhea (23%, 25%); fluid retention events (24%, 32%) such as superficial edema (14%, 16%), pleural effusion (10%, 18%); generalized edema (2%, 1%); congestive heart failure/cardiac dysfunction (0%, 4%); pericardial effusion (1%, 2%); pulmonary edema (0%, 2%); pulmonary hypertension (0%, 1%), and hemorrhage (10%, 14%) including gastrointestinal bleeding (1%, 4%).

In this same study, the frequency of Grade 3/4 neutropenia, thrombocytopenia, and anemia was 34%, 22%, and 10%,
respectively, in the SPRYCEL 100 mg once-daily group and 43%, 38%, and 17%, respectively, in the SPRYCEL 70 mg twice-daily group. The frequency of Grade 3/4 hypophosphatemia and hypocalcemia was 8% and 2%, respectively, in the SPRYCEL 100 mg once-daily group, and 7% and 2%, respectively, in the SPRYCEL 70 mg twice-daily group.

The starting dose for adults with accelerated-phase, myeloid or lymphoid blast-phase CML or adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to prior therapy remains at 70 mg twice daily.

**SPRYCEL and Escalated Doses of Gleevec (Study -017):** The Phase 2 randomized, open-label study evaluated SPRYCEL 70 mg twice daily and Gleevec 800 mg (400 mg twice daily) in 150 patients with chronic-phase CML resistant to prior Gleevec doses of 400 or 600 mg. For patients receiving SPRYCEL, at 12 weeks 36 percent achieved a major cytogenetic response, the study's primary endpoint (29 percent with Gleevec), and 22 percent achieved a complete cytogenetic response (8 percent with Gleevec). With longer treatment and follow-up, 52 percent achieved a major cytogenetic response (33 percent with Gleevec), and 40 percent of patients achieved a complete cytogenetic response (16 percent with Gleevec). The rate of major cytogenetic response with SPRYCEL was lower among patients aged 65 years and over.

At the time of analysis, 39 of 49 patients receiving Gleevec had crossed over to SPRYCEL; 15 of 101 patients receiving SPRYCEL had crossed over to Gleevec. Crossover to alternate therapy was permitted in the event of disease progression or intolerable toxicity. Median duration of treatment prior to crossover was 14 months for SPRYCEL and three months for Gleevec.

Incidence of selected adverse reactions (all grades) in the Phase 2 randomized study in patients receiving SPRYCEL 70 mg twice daily or Gleevec 800 mg daily (400 mg twice daily) included diarrhea (37%, 29%); fluid retention events (36%, 43%) such as pleural effusion (23%, 0%), superficial edema (17%, 41%), generalized edema (2%, 4%), congestive heart failure/cardiac dysfunction (2%, 0%), pericardial effusion (1%, 0%), pulmonary edema (3%, 0%), pulmonary hypertension (1%, 0%); nausea (24%, 33%); hemorrhage (18%, 8%) including gastrointestinal bleeding (3%, 0%), and vomiting (10%, 24%).

In this same study, the frequency of Grade 3/4 neutropenia, thrombocytopenia, and anemia was 63%, 56%, and 19%, respectively, in the SPRYCEL group and 39%, 14%, and 8%, respectively, in the Gleevec group. The frequency of Grade 3/4 hypocalcemia was 4% in the SPRYCEL group and 0% in the Gleevec group.

Patients enrolled in this study received SPRYCEL 70 mg twice daily as described earlier. Per the new labeling, the recommended starting dose for these patients with chronic-phase CML is now 100 mg once daily.

**Cytogenetic and Hematologic Responses**

Major cytogenetic response is defined as complete (0 percent of Philadelphia chromosome-positive [Ph+] cells in the bone marrow) plus partial (less than or equal to 35 percent of Ph+ cells in the bone marrow) cytogenetic responses. Complete hematologic response is a measure of how effective a treatment is in returning blood counts to normal and occurs when blood counts appear normal and patients have no signs or symptoms of disease.

**About SPRYCEL**

On June 28, 2006, the U.S. Food and Drug Administration (FDA) granted accelerated approval of SPRYCEL (pronounced ‘spry-cell’), an oral inhibitor of multiple tyrosine kinases, for the treatment of adults in all three phases of CML (chronic-, accelerated-, or myeloid or lymphoid blast-phase) with resistance or intolerance to prior therapy including Gleevec. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. The FDA also granted full approval of SPRYCEL for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.

Resistance to Gleevec is often due to mutations of BCR-ABL, BCR-ABL overexpression, or activation of new pathways. SPRYCEL is the first approved oral multiple tyrosine kinase inhibitor that, at nanomolar concentrations, inhibits BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRα kinases. SPRYCEL is designed to inhibit the overproduction of leukemia cells in the bone marrow of patients with CML and Ph+ ALL and allows normal red cell, white cell, and blood platelet production to resume.

**IMPORTANT SAFETY INFORMATION**

**Myelosuppression:**

Treatment with SPRYCEL® (dasatinib) is associated with severe CTC Grade 3/4 thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in advanced phase 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. Complete blood counts (CBCs) should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. 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 persistent myelosuppression.

**Bleeding Events:**

Dasatinib caused platelet dysfunction in vitro and thrombocytopenia in humans. Severe CNS hemorrhage, including fatalities, occurred in <1% of patients. Severe GI 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. Caution is advised in patients required to take medications that inhibit platelet function or anticoagulants.

**Fluid Retention:**

Fluid retention was severe in 8% of patients, including pleural and pericardial effusions reported in 5% and 1%, respectively. Severe ascites and generalized edema were reported in <1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion (dyspnea or dry cough) should be evaluated by
QT Prolongation:

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). Nine patients had QTc prolongation as an adverse event. Three patients (<1%) experienced a QTcF >500 msec. SPRYCEL should be administered with caution to patients who have or may develop prolongation of QTc, including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking anti-arrhythmic drugs, other medicinal products that lead to QT prolongation, or cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to SPRYCEL administration.

Drug Interactions:

Dasatinib is a CYP3A4 substrate. Drugs that may increase dasatinib concentrations are: Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, azithromycin, nefazodone, neflinavir, ritonavir, saquinavir, telithromycin, voriconazole). Concomitant use of dasatinib and drugs that inhibit CYP3A4 should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction or temporary discontinuation should be considered. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided. Drugs that may decrease dasatinib concentrations are: Strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). Alternative agents with less enzyme induction potential should be used or a dose increase of SPRYCEL should be considered. St John’s Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided.

Dasatinib is a time-dependent inhibitor of CYP3A4. Drugs that may have their plasma concentration altered by dasatinib are: CYP3A4 substrates such as simvastatin. Therefore, CYP3A4 substrates with a narrow therapeutic index (e.g., alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving SPRYCEL.

Long-term suppression of gastric acid secretion by use of H2 antagonists or proton pump inhibitors (e.g., famotidine and omeprazole) is likely to reduce dasatinib exposure. Therefore, concomitant use of H2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered. Simultaneous administration of SPRYCEL and 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.

Pregnancy:

SPRYCEL 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.

Nursing Mothers:

It is unknown whether SPRYCEL is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug.

Adverse Reactions:

The safety data reflect exposure to SPRYCEL in 2,182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Drug was discontinued for adverse reactions in 9% of patients in chronic phase, 15% in myeloid blast phase CML, and 8% in lymphoid blast phase CML or Ph+ ALL.

The most frequently reported adverse reactions (reported in greater than or equal to 20% of patients) included fluid retention events (37%), diarrhea (31%), headache (24%), skin rash (22%), nausea (22%), hemorrhage (21%), fatigue (21%), and dyspnea (20%).

The most frequently reported serious adverse reactions included pleural effusion (9%), pyrexia (3%), pneumonia (3%), infection (2%), febrile neutropenia (4%), gastrointestinal bleeding (4%), dyspnea (3%), sepsis (1%), diarrhea (2%), congestive heart failure (2%), and pericardial effusion (1%).

Grade 3/4 elevations of transaminase or bilirubin and Grade 3/4 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 phase CML and Ph+ ALL. Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3/4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

Full Prescribing Information is available at [http://www.sprycel.com/](http://www.sprycel.com/).

About Bristol-Myers Squibb

For more than 40 years, Bristol-Myers Squibb has been committed to building a unified vision for the future of cancer treatment. With expertise, dedication and resolve, that vision led to the development of a diverse global portfolio of anti-cancer therapies that are an important cornerstone of care today. Hundreds of scientists in Bristol-Myers Squibb’s Research & Development organization are studying ways to improve current cancer treatments and identify better, more effective medicines for the future. Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

For more information regarding SPRYCEL, please visit [http://www.sprycel.com/](http://www.sprycel.com/).