FDA Grants Full Approval for SPRYCEL® (dasatinib) for the Treatment of Adults with Chronic Myeloid Leukemia Who Are Resistant or Intolerant to Prior Therapies Including Gleevec®*

Release Date:
Tuesday, May 26, 2009 3:00 pm EDT

Terms:
R&D News

Dateline City:
NEW YORK

Two-Year Follow-Up Data Includes 80 Percent Progression-Free Survival Rate in Gleevec-Resistant or Intolerant Patients with Chronic Phase CML

NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has granted full approval for SPRYCEL® (dasatinib) for the treatment of adults in all phases of chronic myeloid leukemia (CML) (chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy including Gleevec®* (imatinib mesylate).

SPRYCEL, an oral tyrosine kinase inhibitor, was originally approved under the accelerated approval regulations of Subpart H for new drugs for serious or life-threatening illnesses of the Food, Drug and Cosmetic Act, based on its effectiveness on hematologic and cytogenetic response rates in CML.

The full approval was based in part on results from a Phase 3 randomized, open-label dose-optimization study that enrolled 670 chronic phase CML patients with resistance or intolerance to Gleevec. The primary endpoint of this study was major cytogenetic response (MCyR) (0-35 percent Ph+ metaphases, which combines both complete and partial responses), in Gleevec-resistant patients. The data included a minimum of two years of follow up after the start of treatment with SPRYCEL 100 mg once daily, which is the recommended starting dose of SPRYCEL for chronic phase CML patients resistant or intolerant to Gleevec. A summary of results from the 167 patients who received SPRYCEL 100 mg once daily include:

- 80 percent progression-free survival (95% CI: 73%-87%) estimated rate at two years, based on Kaplan-Meier estimates
- 91 percent overall survival (95% CI: 86%-96%) estimated rate at two years, based on Kaplan-Meier estimates
- 63 percent of patients achieved MCyR (95% CI: 56%-71%; median duration of treatment was 22 months)
- 93 percent of patients who achieved MCyR maintained that response for 18 months (95% CI: 88%-98%), based on Kaplan-Meier estimates

"SPRYCEL helps to fulfill a need for second-line treatments for CML patients with resistance or intolerance to Gleevec. The two-year follow-up data further support the use of SPRYCEL as an important treatment option for this patient population," said Dr. Hagop Kantarjian, Chairman and Professor, Leukemia Department, MD Anderson Cancer Center.

The approved label also now includes a new recommended starting dosage of SPRYCEL® (dasatinib) 140 mg once daily for accelerated, myeloid blast and lymphoid blast phase CML resistant or intolerant to prior therapy including Gleevec and Ph+ ALL resistant or intolerant to prior therapy.

Safety data in the labeling encompasses results from seven clinical trials and more than 2,100 patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). The most frequently reported serious adverse reactions with SPRYCEL 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 central nervous system (CNS) hemorrhage (1%). The most frequently reported adverse reactions (reported in ≥20% of patients) included myelosuppression, fluid retention events, diarrhea, headache, dyspnea, skin rash, fatigue, nausea and hemorrhage.

About SPRYCEL

On June 28, 2006, the FDA granted accelerated approval of SPRYCEL 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 FDA also granted full approval of SPRYCEL for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.
In vitro

Nursing Mothers: antacids should be avoided. If antacid therapy is needed, with SPRYCEL is not recommended.

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 SPRYCEL 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.

Nursing Mothers:

IMPORTANT SAFETY INFORMATION

Myelosuppression:

Treatment with SPRYCEL® (dasatinib) is associated with severe NCI 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 resistant myelosuppression.

Bleeding Related Events:

SPRYCEL® (dasatinib) caused platelet dysfunction in vitro and thrombocytopenia in humans. Severe central nervous system (CNS) hemorrhage, including fatalities, occurred in 1% of patients. Severe gastrointestinal (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 10% of patients, including pleural and pericardial effusions reported in 7% and 1%, respectively. Severe ascites and generalized edema were each reported in <1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention was typically managed by supportive care measures that included diuretics or short courses of steroids. Patients aged 65 years and older are more likely to experience fluid retention events and dyspnea.

QT Prolongation:

In vitro data suggest that SPRYCEL has the potential to prolong cardiac ventricular repolarization (QT interval). In 865 patients with leukemia from five single-arm studies, the mean changes in QTcF from baseline were 4–6 msec; the upper 95% confidence intervals (CI) for all mean changes from baseline were <7 msec. Of the 2182 patients treated with SPRYCEL in clinical studies, 14 (<1%) patients had QTc prolongation as an adverse reaction. Twenty-one patients (1%) experienced a QTcF >500 msec. SPRYCEL should be administered with caution to patients who have or may develop prolongation of QTc, including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking anti-arrhythmic drugs, other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to SPRYCEL administration.

Pregnancy:

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.

Drug Interactions:

SPRYCEL® (dasatinib) is a CYP3A4 substrate. Drugs that may increase SPRYCEL plasma concentrations are: Strong CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflnavir, ritonavir, saquinavir, telithromycin, voriconazole). Concomitant use of SPRYCEL 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 SPRYCEL and should be avoided. Drugs that may decrease SPRYCEL plasma concentrations are: Strong CYP3A4 Inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital), which should be avoided. 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. St John’s Wort may decrease SPRYCEL plasma concentrations unpredictably and should be avoided.

SPRYCEL is a time-dependent inhibitor of CYP3A4. Drugs that may have their plasma concentration altered by SPRYCEL 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 SPRYCEL 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.
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 the drug.

**Adverse Reactions:**

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

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Drug was discontinued for adverse reactions in 15% of patients in chronic phase, 16% in accelerated phase, 15% in myeloid blast phase, 8% in lymphoid blast phase CML, and 8% in Ph+ ALL.

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

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

Grade 3/4 laboratory abnormalities in chronic phase CML patients who received SPRYCEL 100 mg once daily included neutropenia (36%), thrombocytopenia (23%), anemia (13%), hypophosphatemia (10%) and hypokalemia (2%).

Grade 3/4 elevations of transaminase or bilirubin and Grade 3/4 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 3/4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

Full Prescribing Information is available at www.sprycel.com.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life. For more information, visit www.bms.com.

* Gleevec® is a registered trademark of Novartis AG.

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English

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Ticker: BMY
Exchange: NYSE