FDA Approves SPRYCEL® (dasatinib) as Treatment for Adult Patients with Newly Diagnosed Ph+ Chronic Myeloid Leukemia in Chronic Phase

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In Pivotal DASISION Study, SPRYCEL Demonstrated Superior Efficacy with Higher and Faster Molecular and Confirmed Complete Cytogenetic Response Rates Compared to imatinib by 12 months

SPRYCEL Offers Newly Diagnosed Chronic Phase Ph+ CML Patients Once Daily Dosing Convenience with No Fasting Requirements

PRINCETON, N.J. & TOKYO--(BUSINESS WIRE)--After receiving a priority review, Bristol-Myers Squibb Company (NYSE:BMY) and Otsuka Pharmaceutical Co., Ltd. today announced that the U.S. Food and Drug Administration (FDA) has approved SPRYCEL (dasatinib) 100 mg once daily for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. The trial is ongoing and further data will be required to determine long-term outcome.

The approval was based on results from the DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CP-CML Patients) open-label, Phase 3 trial, which were published in the New England Journal of Medicine and presented as a late-breaking abstract at the 46th Annual Meeting of the American Society of Clinical Oncology in June 2010.

"Data from the DASISION trial demonstrated that newly diagnosed patients with Ph+ CML in chronic phase who received SPRYCEL attained higher and faster molecular and confirmed complete cytogenetic response rates by 12 months compared to imatinib," said Elliott Sigal, M.D., Ph.D., executive vice president, chief scientific officer, and president, Research & Development, Bristol-Myers Squibb. "The FDA approval of SPRYCEL as a first-line treatment for chronic phase CML builds on our commitment to advancing care in hematologic malignancies. Patients now have an option that has both improved response over imatinib, the current standard of care, and offers a once-daily dosing convenience with no fasting requirements."

In the DASISION study, the most frequently reported serious adverse reactions included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%). "SPRYCEL is associated with drug interactions, including use of concomitant strong CYP3A4 inducers, which may decrease plasma concentrations of SPRYCEL and should be avoided. Strong CYP3A4 inhibitors and grapefruit juice may increase plasma concentrations of SPRYCEL and should be avoided. The concomitant use of H2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy. The antacid dose should be given 2 hours before or after SPRYCEL. Tablets should not be crushed or cut; they should be swallowed whole. Please read the Important Safety Information section, including information on Drug Interactions, below.

SPRYCEL Demonstrated Superior Response Rates Compared to imatinib

In the DASISION study, SPRYCEL demonstrated superior efficacy with higher and faster molecular and confirmed cytogenetic response rates compared to imatinib by 12 months in newly diagnosed CP-CML patients. Seventy-seven percent [95% CI: 71.2 – 81.8] of SPRYCEL patients vs. 66% [95% CI: 60.1 – 71.9] of imatinib patients achieved the primary endpoint of confirmed CCyR (two consecutive assessments of CCyR at least 28 days apart) by 12 months (p=0.007†). Median time to confirmed CCyR was 3.1 months in 199 SPRYCEL responders and 5.6 months in 177 imatinib responders. Median time to major molecular response (MMR) was 6.3 months in 135 SPRYCEL responders and 9.2 months in 88 imatinib responders. MMR at any time was higher for SPRYCEL patients (52% [95% CI: 45.9 – 58.3]) versus imatinib (34% [95% CI: 28.1 – 39.9]), p=0.0001†. Transformation to accelerated or blast phase occurred in 5 patients receiving SPRYCEL and 9 patients receiving imatinib.

In this study, the most frequently reported serious adverse reactions included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%). The most frequently reported adverse reactions reported in ≥10% of SPRYCEL patients included myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain, and rash. In patients receiving SPRYCEL, pleural effusion (all grades) was reported in 12%; Grade 3 and 4 pleural effusion was reported in <1% of patients. 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.

About the DASISION Study

DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CP-CML Patients) is an open-label, randomized, Phase 3 international trial of SPRYCEL 100 mg taken once daily vs. imatinib 400 mg taken once daily, in the treatment of newly diagnosed chronic phase Ph+ CML. The study enrolled 519 patients; 259 patients were randomized to receive SPRYCEL and 260 patients were randomized to receive imatinib. The primary study endpoint was the rate of confirmed CCyR by 12 months. Secondary endpoints included time-to confirmed CCyR, MMR rate and time-to MMR.

About SPRYCEL

Discovered and developed by Bristol-Myers Squibb, SPRYCEL initially received accelerated FDA approval in June 2006 as a treatment for adults for all phases of Ph+ CML (chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy including imatinib. Full approval was granted in May 2009. In the imatinib-resistant or -intolerant setting, SPRYCEL is the first and only oral therapy with survival data in the Prescribing Information. SPRYCEL is also approved for the treatment of adults with Ph+ acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

About Chronic Myeloid Leukemia

CML is a slow-growing type of leukemia in which the body produces an uncontrolled number of abnormal white blood cells. About 24,800 people are living with the disease in the United States. It is estimated that 4,870 new cases will be diagnosed in 2010. CML occurs when pieces of two different chromosomes break off and attach to each other. The Philadelphia chromosome contains an abnormal gene called the bcr-abl gene. This gene produces the BCR-ABL protein, which causes your body to make too many abnormal white blood cells. There is no known cause for the genetic change that causes CML.

SPRYCEL® (dasatinib) INDICATIONS & IMPORTANT SAFETY INFORMATION

INDICATIONS

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

- Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of SPRYCEL is based on cytogenetic and major molecular response rates. 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

IMPORTANT SAFETY INFORMATION

Myelosuppression:

- Treatment with SPRYCEL® (dasatinib) can cause severe (NCI CTC Grade 3/4) thrombocytopenia, neutropenia, and anemia, occurring more frequently 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.
  - Perform complete blood counts (CBCs) weekly for the first 2 months and then monthly thereafter, or as clinically indicated
  - Myelosuppression was generally reversible and usually managed by dose interruption, dose reduction, or discontinuation
  - 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
  - In all clinical trials, severe central nervous system (CNS) hemorrhage, including fatalities, occurred in 1% of patients. Severe gastrointestinal (GI) hemorrhage, including fatalities, occurred in 4% of patients receiving SPRYCEL, which generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients
  - Most bleeding events were associated with severe thrombocytopenia
    - Exercise caution in patients required to take medications that inhibit platelet function or anticoagulants

Fluid Retention:

- SPRYCEL is associated with fluid retention
  - In clinical trials fluid retention was severe in up to 10% of patients. Ascites (<1%), generalized edema (<1%), and severe pulmonary edema (1%) were also reported
  - 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
**QT Prolongation:**

- In vitro data suggest that SPRYCEL (dasatinib) has the potential to prolong cardiac ventricular repolarization (QT interval).
- 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.
- In clinical trials of CML patients treated with SPRYCEL (N=2440), 15 patients (<1%) had QTc prolongation as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >500 ms.
- Administer SPRYCEL 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.
  - 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.

**Pregnancy:**

SPRYCEL (dasatinib) 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 when taking SPRYCEL.

**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 SPRYCEL.

**Drug Interactions:**

SPRYCEL is a CYP3A4 substrate and a weak time-dependent inhibitor of CYP3A4.

- Drugs that may increase SPRYCEL plasma concentrations are:
  - **CYP3A4 inhibitors:** Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 should be avoided. If administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction or temporary discontinuation should be considered.
    - **Strong CYP3A4 inhibitors** (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflinavir, ritonavir, saquinavir, telithromycin, voriconazole). If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered.
    - Grapefruit juice may also increase plasma concentrations of SPRYCEL and should be avoided.
  - Drugs that may decrease SPRYCEL plasma concentrations are:
    - **CYP3A4 inducers:** If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered.
    - **Strong CYP3A4 inducers** (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital), should be avoided. Alternative agents with less enzyme induction potential should be considered.
    - **St John’s Wort** may decrease SPRYCEL plasma concentrations unpredictably and should be avoided.
    - **Antacids.** Antacids may decrease SPRYCEL drug levels. 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.
    - **H2 antagonists/proton pump inhibitors,** such as famotidine and omeprazole. Long-term suppression of gastric acid secretion by use of H2 antagonists or proton pump inhibitors is likely to reduce SPRYCEL exposure. Therefore, concomitant use of H2 antagonists or proton pump inhibitors with SPRYCEL is not recommended.

- Drugs that may have their plasma concentration altered by SPRYCEL are:
  - **CYP3A4 substrates** such as simvastatin. CYP3A4 substrates with a narrow therapeutic index should be administered with caution in patients receiving SPRYCEL.

**Adverse Reactions:**

The safety data reflect exposure to SPRYCEL (dasatinib) in 258 patients with newly diagnosed chronic phase CML in a clinical study (median duration of therapy was 18 months) and in 2182 patients with imatinib resistant or intolerant CML or Ph+ ALL in clinical studies (minimum of 2 years follow-up). The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Patients aged 65 years and older are more likely to experience toxicity. In the newly diagnosed chronic phase CML study, SPRYCEL was discontinued for adverse reactions in 6% of patients. In patients resistant or intolerant to prior imatinib therapy, SPRYCEL was discontinued for adverse reactions in 15% patients in chronic phase, 16% in accelerated phase, 15% in myeloid blast phase, 8% in lymphoid blast phase CML, and 8% in Ph+ ALL.

- In newly diagnosed chronic phase CML patients:
  - The most frequently reported serious adverse reactions included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%).
  - The most frequently reported adverse reactions (reported in ≥10% of patients) included myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain, and rash.
- Grade 3/4 laboratory abnormalities included neutropenia (22%), thrombocytopenia (19%), anemia (11%), and hypophosphatemia (5%), hypocalcemia (3%), and elevated bilirubin (1%)

- In patients resistant or intolerant to prior imatinib therapy:
  - 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%)
  - 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
  - Grade 3/4 laboratory abnormalities in chronic phase CML patients resistant or intolerant to prior imatinib therapy who received SPRYCEL 100 mg once daily included neutropenia (36%), thrombocytopenia (23%), anemia (13%), hypophosphatemia (10%), and hypokalemia (2%)
  - Elevation in 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

The full prescribing information is available at www.bms.com.

SPRYCEL is a registered trademark of Bristol-Myers Squibb Company.

About Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.

Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd. are collaborative partners in the commercialization of SPRYCEL in the United States, Japan and major European countries. SPRYCEL was discovered and developed by Bristol-Myers Squibb.

For more information about Bristol-Myers Squibb, visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

Founded in 1964, Otsuka Pharmaceutical Co., Ltd. is a global healthcare company with the corporate philosophy: 'Otsuka—people creating new products for better health worldwide.' Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and consumer products for the maintenance of everyday health. Otsuka is committed to being a corporation that creates global value, adhering to the high ethical standards required of a company involved in human health and life, maintaining a dynamic corporate culture, and working in harmony with local communities and the natural environment. Otsuka Pharmaceutical Co., Ltd. is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group. The Otsuka Group comprises 145 companies and employs approximately 39,000 people in 23 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned ¥1,084.2 billion (approx. US $11.7 billion) in annual revenues in fiscal 2009. Visit Otsuka Pharmaceutical Co., Ltd. at http://www.otsuka.co.jp/en/.

† Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.

†† Major molecular response (MMR) is defined as a BCR-ABL transcript level of ≤0.1% (3 log reduction) as measured by real-time quantitative polymerase chain reaction (RQ-PCR) of peripheral blood.

Language:
English

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