U.S. Food and Drug Administration Accepts Bristol-Myers Squibb’s Application for Sprycel (dasatinib) in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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PRINCETON, N.J.

Application based on results from Phase 2 CA180-372 study

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) accepted its supplemental Biologics License Application (sBLA) for Sprycel (dasatinib) in combination with chemotherapy for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The FDA action date is December 29, 2018.

“Sprycel was first established as an important treatment option for appropriate pediatric patients last year, when it was approved for the treatment of children with Ph+ chronic myeloid leukemia,” said Jeffrey Jackson, Ph.D., development lead, hematology, Bristol-Myers Squibb. “This latest milestone in Ph+ ALL reinforces our commitment to researching the potential of Sprycel in different types of pediatric leukemia and to providing this vulnerable population with access to potential new therapies.”

The application is based on data from CA180-372 (NCT01460160), an ongoing Phase 2 trial evaluating the addition of Sprycel to a chemotherapy regimen modeled on a Berlin-Frankfurt-Munster high-risk backbone in pediatric patients with newly diagnosed Ph+ ALL.

About Sprycel

Sprycel first received FDA approval in 2006 for the treatment of adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) who are resistant or intolerant to prior therapy including imatinib. At that time, Sprycel also received FDA approval for adults with Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to prior therapy. Sprycel is approved and marketed for these indications in more than 60 countries.

Sprycel is also an FDA-approved treatment for adults with newly diagnosed Ph+ CML-CP and is approved for this indication in more than 50 countries.

Both the FDA and the European Commission approved the expansion of Sprycel’s indication to include pediatric patients with Ph+ CML-CP in November 2017 and July 2018.

U.S. FDA-APPROVED INDICATIONS FOR SPRYCEL®

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

- Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase
- 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

SPRYCEL® is indicated for the treatment of pediatric patients with:

- Ph+ CML in chronic phase

IMPORTANT SAFETY INFORMATION

Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTCAE Grade 3/4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with 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 with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated
- In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated
- Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction
  - In clinical studies, myelosuppression may have also been managed by discontinuation of study therapy
  - Hematopoietic growth factor has been used in patients with resistant myelosuppression

**Bleeding-Related Events**

SPRYCEL can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal.

- Most bleeding events in clinical studies were associated with severe thrombocytopenia
- In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*
- Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage

**Fluid Retention**

SPRYCEL may cause fluid retention. After 5 years of follow-up in the adult randomized newly diagnosed chronic phase CML study (n=258), grade 3/4 fluid retention was reported in 5% of patients, including 3% of patients with grade 3/4 pleural effusion. In adult patients with newly diagnosed or imatinib resistant or intolerant chronic phase CML, grade 3/4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In adult patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), grade 3/4 fluid retention was reported in 8% of patients, including grade 3/4 pleural effusion reported in 7% of patients. In pediatric patients with chronic phase CML cases of Grade 1 or 2 fluid retention were reported in 10.3% of patients.

- Patients who develop symptoms of pleural effusion or other fluid retention, such as new or worsened dyspnea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with a chest x-ray or additional diagnostic imaging as appropriate
- Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids
- Severe pleural effusion may require thoracentesis and oxygen therapy
- Consider dose reduction or treatment interruption

**Cardiovascular Events**

SPRYCEL can cause cardiac dysfunction. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial in adults (n=258), the following cardiac adverse reactions occurred:

- Cardiac ischemic events (3.9% dasatinib vs 1.6% imatinib), cardiac related fluid retention (8.5% dasatinib vs 3.9% imatinib), and conduction system abnormalities, most commonly arrhythmia and palpitations (7.0% dasatinib vs 5.0% imatinib). Two cases (0.8%) of peripheral arterial occlusive disease occurred with imatinib and 2 (0.8%) transient ischemic attacks occurred with dasatinib

Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

**Pulmonary Arterial Hypertension (PAH)**

SPRYCEL may increase the risk of developing PAH in adult and pediatric patients, which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of SPRYCEL.

- Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL and during treatment. If PAH is confirmed, SPRYCEL should be permanently discontinued

**QT Prolongation**

SPRYCEL may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy

- Correct hypokalemia or hypomagnesemia prior to and during SPRYCEL administration

**Severe Dermatologic Reactions**

Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in patients treated with SPRYCEL.
• Discontinue permanently in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified

**Tumor Lysis Syndrome (TLS)**

TLS has been reported in patients with resistance to prior imatinib therapy, primarily in advanced phase disease.

• Due to potential for TLS, maintain adequate hydration, correct uric acid levels prior to initiating therapy with SPRYCEL, and monitor electrolyte levels
• Patients with advanced stage disease and/or high tumor burden may be at increased risk and should be monitored more frequently

**Embryo-Fetal Toxicity**

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Hydrops fetalis, fetal leukopenia and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Transplacental transfer of dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma.

• Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with SPRYCEL and for 30 days after the final dose

**Effects on Growth and Development in Pediatric Patients**

In pediatric trials of SPRYCEL in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia. Of these 5 cases, 1 case of osteopenia and 1 case of gynecomastia resolved during treatment.

**Lactation**

No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed child or the effects of the drug on milk production. However, dasatinib is present in the milk of lactating rats.

• Because of the potential for serious adverse reactions in nursing children from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose

**Drug Interactions**

• **Strong CYP3A4 inhibitors:** The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction
  • **Grapefruit juice** may increase plasma concentrations of SPRYCEL and should be avoided
• **Strong CYP3A4 inducers:** The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase
  • **St. John’s wort** may decrease plasma concentrations of SPRYCEL and should be avoided
• **Gastric Acid Reducing Agents:** The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.
  
  Do not administer H2 antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

**Adverse Reactions**

The safety data reflects exposure to SPRYCEL at all doses tested in clinical studies (n=2809) including 324 adult patients with newly diagnosed chronic phase CML, 2388 adult patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+ ALL, and 97 pediatric patients with chronic phase CML.

The median duration of therapy in a total of 2712 SPRYCEL-treated adult patients was 19.2 months (range 0–93.2 months). Median duration of therapy in:

• 1618 adult patients with chronic phase CML was 29 months (range 0–92.9 months)
  • Median duration for 324 adult patients in the newly diagnosed chronic phase CML trial was approximately 60 months
  • 1094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months)

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

In the newly diagnosed adult chronic phase CML trial, after a minimum of 60 months of follow-up, the cumulative discontinuation rate for 258 patients was 39%.

In the overall population of 2712 adult SPRYCEL-treated patients, 88% of patients experienced adverse reactions at some
time and 19% experienced adverse reactions leading to treatment discontinuation.

Among the 1618 adult SPRYCEL-treated patients with chronic phase CML, drug-related adverse reactions leading to discontinuation were reported in 329 (20.3%) patients.

- In the adult newly diagnosed chronic phase CML trial, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up.

Among the 1094 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

Among the 97 pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

Patients ≥65 years are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema and weight decrease, and should be monitored closely.

- In adult newly diagnosed chronic phase CML patients:
  - Drug-related serious adverse reactions (SARs) were reported for 16.7% of patients. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%)
  - Grade 3/4 laboratory abnormalities included neutropenia (29%), thrombocytopenia (22%), anemia (13%), hypophosphatemia (7%), hypocalcemia (4%), elevated bilirubin (1%), and elevated creatinine (1%)

- In adult patients resistant or intolerant to prior imatinib therapy:
  - Drug-related SARs were reported for 26.1% of SPRYCEL-treated patients treated at the recommended dose of 100 mg once daily in the randomized dose-optimization trial of patients with chronic phase CML resistant or intolerant to prior imatinib therapy. Serious adverse reactions reported in ≥5% of patients included pleural effusion (10%)
  - Grade 3/4 hematologic laboratory abnormalities in chronic phase CML patients resistant or intolerant to prior imatinib therapy who received SPRYCEL 100 mg once daily with a minimum follow up of 60 months included neutropenia (36%), thrombocytopenia (24%), and anemia (13%). Other grade 3/4 laboratory abnormalities included: hypophosphatemia (10%), and hypokalemia (2%)
  - Among chronic phase CML patients with resistance or intolerance to prior imatinib therapy, cumulative grade 3/4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%)

- Grade 3/4 elevations of transaminases or bilirubin and Grade 3/4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML
  - Elevations in transaminases 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

- In pediatric subjects with Ph+ CML in chronic phase
  - Drug-related SARs were reported for 14.4% of pediatric patients
  - In the pediatric studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults

- Most common adverse reactions (≥15%) in patients included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain

Please see full Prescribing Information here.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that Sprycel will receive regulatory approval for an additional indication described herein. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2017 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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