Early, Durable Responses Seen with Sprycel (dasatinib) in First- and Second-Line Treatment of Pediatric Patients with Chronic Myeloid Leukemia in Chronic Phase (CP-CML)

Target responses were sustained over time in newly diagnosed and imatinib-resistant or -intolerant pediatric patients and treatment safety profile was comparable to that in adult patients

Largest prospective trial in pediatric chronic myeloid leukemia in chronic phase includes first formulation specifically developed for pediatric population

Study CA180-226

CA180-226 is an ongoing Phase 2, open-label, nonrandomized study evaluating Sprycel in patients aged 18 years or younger
with newly diagnosed chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) leukemias resistant to or intolerant of imatinib. Cohorts 1 and 3 examined 29 CP-CML pediatric patients resistant to or intolerant of imatinib and 84 pediatric patients with newly diagnosed CML in chronic phase (CP), respectively. Cohort 2 evaluated Sprycel® in pediatric patients with accelerated/blast phase CML or Philadelphia chromosome-positive acute lymphoblastic leukemia.

Patients newly diagnosed with CP-CML received either Sprycel® 60 mg/m² tablets orally, once daily, or 72 mg/m² Sprycel® powder for oral suspension (PFOS) once daily, and patients with CP-CML resistant to or intolerant of imatinib also received Sprycel® tablets 60 mg/m² orally, once daily.

One patient had a Sprycel®-related AE leading to discontinuation, and one patient died from gastrointestinal bleeding unrelated to treatment. The most commonly reported AEs in newly diagnosed patients treated with Sprycel were nausea/vomiting (20%), rash (19%) and diarrhea (18%), and in imatinib-intolerant or -resistant patients were nausea/vomiting (31%), myalgia/arthralgia (17%), fatigue (14%) and rash (14%).

**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® was also approved for adults with Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to prior therapy. Sprycel® is approved and marketed worldwide for these indications in more than 60 countries.

Sprycel® is also an FDA-approved treatment for adults with newly diagnosed CP Ph+ CML (since October 2010). Sprycel® received accelerated FDA approval for this indication. Additional country approvals for this indication total more than 50.

**U.S. FDA-APPROVED INDICATIONS FOR SPRYCEL®**

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

- Newly diagnosed adults with 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.

**IMPORTANT SAFETY INFORMATION**

**Myelosuppression**

Treatment with SPRYCEL® is associated with severe (NCI CTC 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® caused thrombocytopenia in human subjects. In addition, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, ≥grade 3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL®. Grade 3 or greater gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of ≥grade 3 hemorrhage occurred in 2% of patients.

- Most bleeding events in clinical studies were associated with severe thrombocytopenia.
- 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 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 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 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.

- 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**

After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial (n=258), the following cardiac adverse events 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, 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**

*In vitro* data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval).

- In clinical trials of patients treated with SPRYCEL at all doses (n=2440), 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >500 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 to 13.4 ms.
- 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.

**Lactation**

No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed infant 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 infants from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose.

**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 should be considered.

**Strong CYP3A4 inhibitors** (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease 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:**

- **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. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity.

- **St John’s Wort** may decrease SPRYCEL plasma concentrations unpredictably and should be avoided.

**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** (eg, 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** (eg, simvastatin) with a narrow therapeutic index should be administered with caution in patients receiving SPRYCEL.

## Adverse Reactions

The safety data reflects exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and 2388 patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+ ALL.

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

- 1618 patients with chronic phase CML was 29 months (range 0–92.9 months)
- 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months)

In the newly diagnosed 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 SPRYCEL-treated patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

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

- In the 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 events leading to discontinuation were reported in 191 (17.5%) patients.

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 newly diagnosed chronic phase CML patients:
  - Drug-related serious adverse events (SAEs) were reported for 16.7% of SPRYCEL-treated patients. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%).
  - The most common adverse reactions (≥15%) included myelosuppression, fluid retention, and diarrhea.
  - Grade 3/4 laboratory abnormalities included neutropenia (29%), thrombocytopenia (22%), anemia (13%), hypophosphatemia (7%), hypocalcemia (4%), elevated bilirubin (1%), and elevated creatinine (1%).

- In patients resistant or intolerant to prior imatinib therapy:
  - Drug-related SAEs 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%).
  - The most common adverse reactions (≥15%) included myelosuppression, fluid retention events, diarrhea, headache, fatigue, dyspnea, skin rash, nausea, hemorrhage and musculoskeletal pain.
  - 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.

Please see the full Prescribing Information for SPRYCEL.

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, 2016 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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