Seven-year study matches the longest duration of follow-up for any CML treatment, including imatinib, based on approved prescribing information

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) and Otsuka America Pharmaceutical, Inc. today announced that the U.S. Food and Drug Administration (FDA) has approved an update to the Sprycel® (dasatinib) product labeling. The labeling now includes five-year efficacy and safety data in adult patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) and seven-year data in CP Ph+ CML patients who are resistant 1 or intolerant 2 to prior therapy, including Gleevec® 3 (imatinib mesylate).

“The five- and seven-year data now included in the Sprycel U.S. label offer valuable insight into its long-term efficacy and safety profile in both first- and second-line patients,” said Neil Shah, MD, PhD, Associate Professor, Division of Hematology/Oncology, University of California, San Francisco. “CML requires ongoing treatment and assessment of treatment milestones in order to manage the disease properly. Given the chronic nature of CML, these long-term data are particularly important for patient care.”

Sprycel is associated with the following warnings and precautions: myelosuppression, bleeding-related events, fluid retention, cardiovascular events, pulmonary arterial hypertension, QT prolongation, severe dermatologic reactions, tumor lysis syndrome, and embryo-fetal toxicity. Please see detailed Important Safety Information below.

“Treating CML across the spectrum of the disease has been an important focus for Bristol-Myers Squibb and Otsuka, and we remain committed to helping newly diagnosed and imatinib-resistant or intolerant CP Ph+ CML patients through treatment with Sprycel, a convenient once-daily treatment option,” said Laura Bessen, MD, Vice President, head of U.S. Medical, Bristol-Myers Squibb. “We are proud to have generated this important five- and seven-year data in the first- and second-line treatment of CP Ph+ CML, as the findings further support the overall efficacy and safety profile of Sprycel over the long-term.”

About the DASISION Study (CA180-056)

DASISION is an open-label, randomized, Phase 3 international trial of Sprycel 100 mg tablet taken once-daily (n=259) vs. imatinib 400 mg taken once-daily (n=260) in the treatment of newly-diagnosed CP Ph+ CML. The primary study endpoint was confirmed CCyR 4 by 12 months and secondary endpoints included MMR 5 at any time, time to MMR, and time to confirmed CCyR. With a minimum of five years follow-up, 61% of Sprycel patients and 62% of imatinib patients were still on treatment at the time of final analysis.

In DASISION, 77% [95% CI, 71% - 82%] of patients treated with Sprycel vs. 66% [95%, CI, 60% - 72%] of patients treated with imatinib achieved the primary endpoint of confirmed CCyR (defined as two consecutive assessments of CCyR at least 28 days apart) by 12 months (p=0.007). After five years of follow-up, median time to confirmed CCyR was 3.1 months in 215 Sprycel responders and 5.8 months in 204 imatinib responders 7. In the long-term (by 5 years), confirmed CCyR rates were 83% Sprycel vs. 79% imatinib.

Sprycel patients were more likely than imatinib patients to achieve MMR, a measure of deeper treatment response, by year one (52% [95% CI, 46% - 58%] vs. 34% [95% CI, 28% - 40%], respectively; p<0.0001). In the long-term (by year 5), MMR at any time was higher for Sprycel than imatinib (76% [95% CI, 71% - 82%] vs 64% [95% CI, 58% - 70%], respectively). At 60 months follow-up, in the Sprycel arm, the rate of MMR at any time in each risk group determined by Hasford score (a prognostic scoring system) was 90% (low risk), 71% (intermediate risk) and 67% (high risk). In the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk) and 54% (high risk). The five-year data for confirmed CCyR and MMR demonstrate the long-lasting efficacy of Sprycel.

At five years, eight patients (3%) in the Sprycel arm progressed to either accelerated phase or blast crisis while 15 patients...
About Chronic Myeloid Leukemia

CML is a type of leukemia in which the body produces an uncontrolled number of abnormal white blood cells. According to the most recent statistics, about 33,990 people are living with the disease in the United States. An estimated 6,660 new cases were diagnosed in 2014. CML occurs when pieces of two different chromosomes (chromosomes 9, 22) break off and attach to each other. The newly formed chromosome is called the Philadelphia chromosome, which contains an abnormal gene called the BCR-ABL gene. This gene produces the BCR-ABL protein that signals cells to make too many white blood cells. There is no known cause for the genetic change that results in CML.

About Sprycel® (dasatinib)

Sprycel was first approved by the FDA in 2006 for the treatment of adults with CP Ph+ CML who are resistant or intolerant to prior therapy including imatinib. At that time, Sprycel was also approved for adults with Ph+ ALL who are resistant or intolerant to prior therapy. It is the first and only BCR-ABL kinase inhibitor with survival data in its label for CP Ph+ CML patients who are resistant or intolerant to imatinib. 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.

SPRYCEL® (dasatinib) INDICATIONS & IMPORTANT SAFETY INFORMATION

INDICATIONS

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

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.

- 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:

- 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%).
Most common adverse reactions (≥15%) included myelosuppression, fluid retention, and diarrhea.

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

Please see full Prescribing Information here.

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.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global pharmaceutical 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 www.bms.com, or follow us on Twitter at http://twitter.com/bmsnews.

About Otsuka

Otsuka Pharmaceutical, headquartered in Japan, is a leading firm in the challenging area of mental health and also has products and research programs for several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate more powerfully than words how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does.

In the U.S., Otsuka America Pharmaceutical, Inc. commercializes Otsuka-discovered and in-licensed products, with a focus on neuroscience, oncology, cardio-renal, and medical devices.


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. 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, 2014 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.

Endnotes:

1. Resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response.

2. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

3. Gleevec is a registered trademark of Novartis AG.

4. Complete cytogenetic response (CCyR) is defined as the absence of Philadelphia chromosome-positive metaphases on cytogenetic assessment of bone marrow cells.

5. 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. These are cumulative rates representing minimum follow-up for the timeframe specified.

6. CI=confidence interval

7. Formal statistical comparison of cCCyR and MMR rates was only performed at the time of the primary endpoint (cCCyR within 12 months).
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Contact:
Bristol-Myers Squibb
Media:
Shelly Mittendorf, 609-897-2055
cell: 609-480-2951
shelly.mittendorf@bms.com
or
Investors:
Ranya Dajani, 609-252-5330
cell: 215-666-1515
ranya.dajani@bms.com
or
William Szablewski, 609-252-5894
cell: 215-801-0906
william.szablewski@bms.com
or
Otsuka
Media:
Kimberly Whitefield, 609-535-9259
cell: 201-738-7130
kimberly.whitefield@otsuka-us.com

Ticker Slug:
Ticker: BMY
Exchange: NYSE