14 Feb 2017

Direct Healthcare Professional Communication on Updated Prescribing Safety Information for SPRYCEL® (dasatinib)

Dear Healthcare Professional,

Bristol Myers Squibb (BMS) in agreement with the Egyptian Pharmaceutical Egyptian Center (EPVC) would like to inform you about important new safety information for SPRYCEL(Dasatinib).

Summary:

The following are the different sections of the prescribing information with the most significant modifications/changes/new safety information that could impact the management of CMLpatients:

Section 2: DOSAGE AND ADMINISTRATION

The recommended starting dosage of SPRYCELfor chronic phase CML is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg administered orally once daily. Tablets should not be crushed or cut; they should be swallowed whole. SPRYCELcan be taken with or without a meal, either in the morning or in the evening.

In clinical studies, treatment with SPRYCELwas continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response [CCyRJ) or major molecular response (MMR) is not known.

Section 5: Warnings and Precautions

Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 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 SPRYCELtemporarily and/or dose reduction.

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Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, 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

SPRYCELmay cause fluid retention. After 5 years of follow-up in the randomized newly diagnosed chronic phase CMLstudy (n=258), grade 3 or 4 fluid retention was reported in 5% of patients, including 3% of patients with grade 3 or 4 pleural effusion. In patients with newly diagnosed or imatinib-resistant or –intolerant chronic phase CML, grade 3 or 4 fluid retention occurred in 6% of patients treated with SPRYCELat the recommended dose (n=548). In patients with advanced phase CMLor Ph+ ALL treated with SPRYCELat the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural effusion reported in 7% of patients.
Evaluate 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, 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

SPRYCELmay increase the risk of developing pulmonary arterial hypertension (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

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

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). Of the 2440 patients treated with SPRYCEL at all doses tested in clinical studies, 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 SPRYCELin five Phase 2 single-arm studies, the maximum mean changes in QTcF (90% upper bound Cl) from baseline ranged from 7.0 ms to 13.4 ms.

SPRYCELmay increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal productsthat 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

Tumor lysis syndrome has been reported in patients with resistance to prior imatinib therapy, primarily in advanced phase disease. Due to potential for tumor lysis syndrome, 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, SPRYCELcan cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of SPRYCELincluding hydrops fetalis, fetal ieukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL.Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with SPRYCELand for 30 days after the final dose.

Section 8: Use in Specific Populations

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Pregnancy

Risk Summary

Based on limited human data, SPRYCELcan cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL.Animal reproduction studies in rats have demonstrated extensive mortality during organogenesis, the fetal period, and in neonates. Skeletal malformations were observed in a limited number of surviving rat and rabbit conceptuses. These findings occurred at dasatlnib plasma concentrations below those in humans receiving therapeutic doses of dasatinib [see Data]. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Transplacental transfer of dasatinib has been reported. Dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma. Hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to dasatinib. These adverse pharmacologic effects on the fetus are similar to *adverse* reactions observed in adult patients and may result in fetal harm or neonatal death.

Lactation

Risk Summary

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 SPRYCELand for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

SPRYCELcan cause fetal harm when administered to a preqnant woman [see Use in Specific Populations]. Advise females of reproductive potential to *avoid* pregnancy, which may include the use of effective contraceptive methods, during treatment with SPRYCELand for 30 days after the final dose.

Infertility

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Based on animal data, dasatinib may result in damage to female and male reproductive tissues.

Geriatric Use

No differences in confirmed Complete Cytogenetic Response (cCCyR) and MMR were observed between older and younger patients. Of the 2712 patients in clinical studies of SPRYCEL,617 (23%) were 65 years of age and older, and 123 (5%) were 75 years of age and older. While the safety profile of SPRYCELin the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adversereactions 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.

Further information on recommendations to healthcare professionals

SPRYCEL(dasatinib) is an oral tyrosine kinase inhibitor indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or myeloid or lymphoid blast Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

It is strongly recommended that HCPs discuss this updated information with their patients whether on treatment with (or recently prescribed/switched) to SPRYCEL (Dasatinib).

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