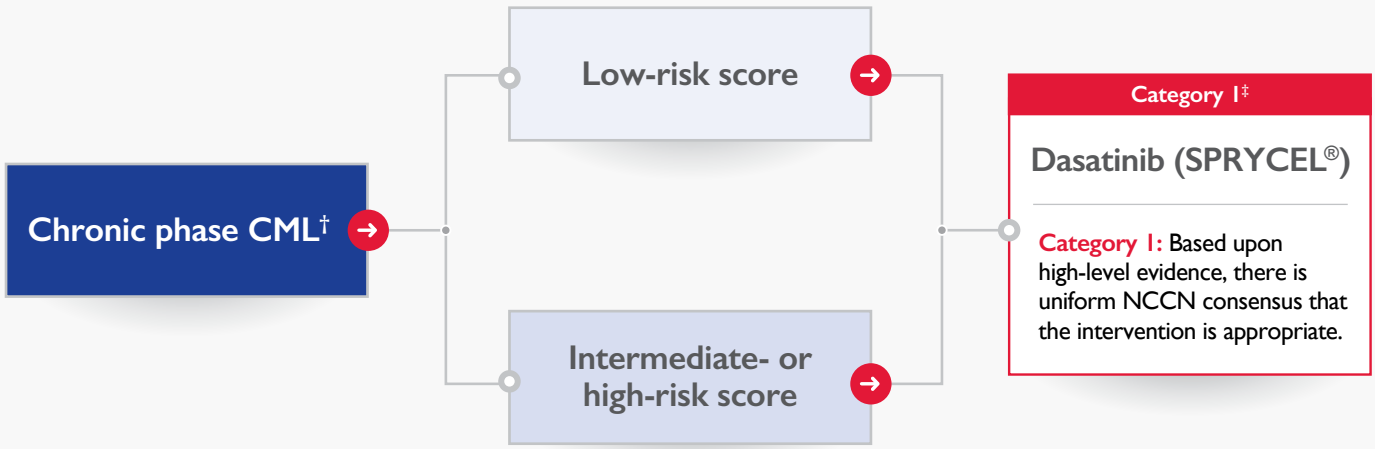
In newly diagnosed adults with Ph+ CML in CP[1]

Dasatinib (SPRYCEL®) is a Category 1 Preferred National Comprehensive Cancer Network® (NCCN®) Treatment Recommendation[2]*



CP=chronic phase.

*NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.
†Please see NCCN guidelines for additional treatment considerations.
‡Please see NCCN guidelines for specific recommendations.

Dasatinib (SPRYCEL®): An NCCN Category 1 treatment recommendation regardless of risk score[2‡]

INDICATION

SPRYCEL® (dasatinib) is indicated for the treatment of adult patients with:
- Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (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
- 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 patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of 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 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).

- 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

(Continued on next page)

Please see additional Important Safety Information on the following page and full Prescribing Information for SPRYCEL.

IMPORTANT SAFETY INFORMATION (cont'd)

Cardiovascular Toxicity:

SPRYCEL® can cause cardiac dysfunction. After 5 years of follow-up in the randomized, newly diagnosed chronic phase CML trial (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, 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 and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose

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 last dose

Drug Interactions:

Effect of Other Drugs on Dasatinib

- **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 H_2 antagonists or proton pump inhibitors with SPRYCEL
  Consider the use of antacids in place of H_2 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 doses tested in clinical studies (n=2712) including 324 patients with newly diagnosed chronic phase CML and 2388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase Ph+ CML or Ph+ ALL.

The median duration of therapy in a total of 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)
  - Median duration for 324 patients in the newly diagnosed chronic phase CML trial was approximately 60 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 reactions 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

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 reactions (SARs) 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%)
- 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 full Prescribing Information for SPRYCEL.

References: 1. SPRYCEL full Prescribing Information. Bristol-Myers Squibb Company; 2021. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed September 12, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

729-US-2100443 09/21