**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use SPRYCEL safely and effectively. See full prescribing information for SPRYCEL.**

**SPRYCEL® (dasatinib) tablets, for oral use**
**Initial U.S. Approval: 2006**

**----------INDICATIONS AND USAGE----------**

**SPRYCEL is a kinase inhibitor indicated for the treatment of**

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)

**----------DOSAGE AND ADMINISTRATION----------**

- Chronic phase CML: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL: 140 mg once daily. (2)
- Administer orally, with or without a meal. Do not crush or cut. (2)

**----------DOSAGE FORMS AND STRENGTHS----------**

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg. (3, 16)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- *Myelosuppression and Bleeding Events:* Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated. (2.3, 5.1, 5.2, 6.1)
- *Fluid Retention:* Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification. (2.3, 5.3, 6.1)
- *Cardiac Dysfunction:* Monitor patients for signs or symptoms and treat appropriately. (5.4, 6.1)
- *Pulmonary Arterial Hypertension (PAH):* SPRYCEL may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed. (5.5)
- *QT Prolongation:* Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.6)
- *Severe Dermatologic Reactions:* Individual cases of severe mucocutaneous dermatologic reactions have been reported. (5.7, 6.4)
- *Tumor Lysis Syndrome:* Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL. (5.8)
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise of potential risk to fetus and avoid pregnancy. (5.9, 8.1, 8.3)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (≥15%) in patients with newly diagnosed chronic phase CML included myelosuppression, fluid retention, and diarrhea. Most common adverse reactions (≥15%) in patients with resistance or intolerance to prior imatinib therapy included myelosuppression, fluid retention events, diarrhea, headache, fatigue, dyspnea, skin rash, nausea, hemorrhage, and musculoskeletal pain. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

- *CYP3A4 Inhibitors:* May increase dasatinib drug levels; dose reduction may be necessary. (2.1, 7.1)
- *CYP3A4 Inducers:* May decrease dasatinib drug levels; dose increase may be necessary. (2.1, 7.2)
- *Antacids:* May decrease dasatinib drug levels; avoid simultaneous administration. (7.2)
- $H_2$ *Antagonists/Proton Pump Inhibitors:* May decrease dasatinib drug levels. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**

- *Lactation:* Not recommended (8.2)
- *Hepatic Impairment:* Use SPRYCEL with caution in patients with hepatic impairment. (8.6)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 09/2016**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

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.

## 2 DOSAGE AND ADMINISTRATION

The recommended starting dosage of SPRYCEL for 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. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

In clinical studies, treatment with SPRYCEL was 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 [CCyR]) or major molecular response (MMR) is not known.

### 2.1 Dose Modification

**Concomitant Strong CYP3A4 inducers:** The use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John's wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, a SPRYCEL dose increase should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity *[see Drug Interactions (7.2)]*.

**Concomitant Strong CYP3A4 inhibitors:** CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible, is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered. Based on pharmacokinetic studies, a dose decrease to 20 mg daily should be considered for patients taking SPRYCEL 100 mg daily. For patients taking SPRYCEL 140 mg daily, a dose decrease to 40 mg daily should be

considered. These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors. However, there are no clinical data with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either the strong CYP3A4 inhibitor must be discontinued, or SPRYCEL should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the SPRYCEL dose is increased *[see Drug Interactions (7.1)]*.

## 2.2 Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

## 2.3 Dose Adjustment for Adverse Reactions

### Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 1.

**Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia**

| | | |
|---|---|---|
| Chronic Phase CML<br>(starting dose 100 mg once daily) | ANC* $<0.5 \times 10^9$/L<br>or<br>Platelets $<50 \times 10^9$/L | 1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L.<br>2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days.<br>3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib). |

**Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia**

| | | |
|---|---|---|
| Accelerated Phase CML, Blast Phase CML and Ph+ ALL<br>(starting dose 140 mg once daily) | ANC* $<0.5 \times 10^9$/L<br>or<br>Platelets $<10 \times 10^9$/L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy).<br>2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose.<br>3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).<br>4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily. |

*ANC: absolute neutrophil count

### Non-hematological Adverse Reactions

If a severe non-hematological adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event *[see Warnings and Precautions (5.1)]*.

## 3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, 80-mg, 100-mg, and 140-mg white to off-white, biconvex, film-coated tablets *[see How Supplied (16.1)]*.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 SPRYCEL temporarily and/or dose reduction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

## 5.2 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.

## 5.3 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 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 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 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 *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

## 5.4 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.

## 5.5 Pulmonary Arterial Hypertension

SPRYCEL may 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 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.

### 5.6 QT Prolongation

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

### 5.7 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.

### 5.8 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 *[see Adverse Reactions (6.3)]*.

### 5.9 Embryo-Fetal Toxicity

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of SPRYCEL including hydrops fetalis, fetal leukopenia, 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 SPRYCEL and for 30 days after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Myelosuppression *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Bleeding-related events *[see Warnings and Precautions (5.2)]*.
- Fluid retention *[see Warnings and Precautions (5.3)]*.
- Cardiovascular events *[see Warnings and Precautions (5.4)]*.
- Pulmonary arterial hypertension *[see Warnings and Precautions (5.5)]*.
- QT prolongation *[see Warnings and Precautions (5.6)]*.
- Severe dermatologic reactions *[see Warnings and Precautions (5.7)]*.
- Tumor lysis syndrome *[see Warnings and Precautions (5.8)]*.
- Embryo-fetal toxicity *[see Warnings and Precautions (5.9)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and in 2388 patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL-treated patients was 19.2 months (range 0–93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1618 patients with chronic phase CML was 29 months (range 0–92.9 months).

The median duration of therapy in 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months).

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.

In the randomized trial in patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 39%. Among the 1618 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 329 (20.3%) patients; 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.

Adverse reactions reported in ≥10% of patients, and other adverse reactions of interest, in a randomized trial in patients with newly diagnosed chronic phase CML at a median follow-up of approximately 60 months are presented in Table 2.

Adverse reactions reported in ≥10% of patients treated at the recommended dose of 100 mg once daily (n=165), and other adverse reactions of interest, in a randomized dose-optimization trial of

patients with chronic phase CML resistant or intolerant to prior imatinib therapy at a median follow-up of approximately 84 months are presented in Table 4.

Drug-related serious adverse events (SAEs) were reported for 16.7% of SPRYCEL-treated patients in the randomized trial of patients with newly diagnosed chronic phase CML. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%).

Drug-related SAEs were reported for 26.1% of 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%).

## 6.1 Chronic Myeloid Leukemia (CML)

Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of patients are shown in Table 2 for newly diagnosed patients with chronic phase CML and Tables 4 and 6 for CML patients with resistance or intolerance to prior imatinib therapy.

**Table 2: Adverse Reactions Reported in ≥10% of Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)**

| | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | **SPRYCEL (n=258)** | **Imatinib (n=258)** | **SPRYCEL (n=258)** | **Imatinib (n=258)** |
| **Preferred Term** | **Percent (%) of Patients** | | | |
| Fluid retention | 38 | 45 | 5 | 1 |
| Pleural effusion | 28 | 1 | 3 | 0 |
| Superficial localized edema | 14 | 38 | 0 | <1 |
| Pulmonary hypertension | 5 | <1 | 1 | 0 |
| Generalized edema | 4 | 7 | 0 | 0 |
| Pericardial effusion | 4 | 1 | 1 | 0 |
| Congestive heart failure/ cardiac dysfunction[a] | 2 | 1 | <1 | <1 |
| Pulmonary edema | 1 | 0 | 0 | 0 |
| Diarrhea | 22 | 23 | 1 | 1 |
| Musculoskeletal pain | 14 | 17 | 0 | <1 |
| Rash[b] | 14 | 18 | 0 | 2 |
| Headache | 14 | 11 | 0 | 0 |
| Abdominal pain | 11 | 8 | 0 | 1 |
| Fatigue | 11 | 12 | <1 | 0 |
| Nausea | 10 | 25 | 0 | 0 |
| Myalgia | 7 | 12 | 0 | 0 |
| Arthralgia | 7 | 10 | 0 | <1 |
| Hemorrhage[c] | 8 | 8 | 1 | 1 |
| Gastrointestinal bleeding | 2 | 2 | 1 | 0 |

**Table 2: Adverse Reactions Reported in ≥10% of Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)**

| | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | SPRYCEL (n=258) | Imatinib (n=258) | SPRYCEL (n=258) | Imatinib (n=258) |
| **Preferred Term** | **Percent (%) of Patients** | | | |
| Other bleeding[d] | 6 | 6 | 0 | <1 |
| CNS bleeding | <1 | <1 | 0 | <1 |
| Vomiting | 5 | 12 | 0 | 0 |
| Muscle spasms | 5 | 21 | 0 | <1 |

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

[c] Adverse reaction of special interest with <10% frequency.

[d] Includes conjunctival hemorrhage, ear hemorrhage, ecchymosis, epistaxis, eye hemorrhage, gingival bleeding, hematoma, hematuria, hemoptysis, intra-abdominal hematoma, petechiae, scleral hemorrhage, uterine hemorrhage, and vaginal hemorrhage.

A comparison of cumulative rates of adverse reactions reported in ≥10% of patients with minimum follow-up of 1 and 5 years in a randomized trial of newly diagnosed patients with chronic phase CML treated with SPRYCEL are shown in Table 3.

**Table 3: Adverse Reactions Reported in ≥10% of Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)**

| | Minimum of 1 Year Follow-up | | Minimum of 5 Years Follow-up | |
|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| **Preferred Term** | **Percent (%) of Patients** | | | |
| Fluid retention | 19 | 1 | 38 | 5 |
| Pleural effusion | 10 | 0 | 28 | 3 |
| Superficial localized edema | 9 | 0 | 14 | 0 |
| Pulmonary hypertension | 1 | 0 | 5 | 1 |
| Generalized edema | 2 | 0 | 4 | 0 |
| Pericardial effusion | 1 | <1 | 4 | 1 |
| Congestive heart failure/cardiac dysfunction[a] | 2 | <1 | 2 | <1 |
| Pulmonary edema | <1 | 0 | 1 | 0 |
| Diarrhea | 17 | <1 | 22 | 1 |
| Musculoskeletal pain | 11 | 0 | 14 | 0 |
| Rash[b] | 11 | 0 | 14 | 0 |
| Headache | 12 | 0 | 14 | 0 |

**Table 3: Adverse Reactions Reported in ≥10% of Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)**

| | | | | |
|---|---|---|---|---|
| Abdominal pain | 7 | 0 | 11 | 0 |
| Fatigue | 8 | <1 | 11 | <1 |
| Nausea | 8 | 0 | 10 | 0 |

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%); 1 death in each group was assessed by the investigator as related to study therapy.

**Table 4: Adverse Reactions Reported in ≥10% of Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)**

| | 100 mg Once Daily | |
|---|---|---|
| | Chronic (n=165) | |
| | All Grades | Grade 3/4 |
| **Preferred Term** | Percent (%) of Patients | |
| Fluid retention | 48 | 7 |
| Superficial localized edema | 22 | 0 |
| Pleural effusion | 28 | 5 |
| Generalized edema | 4 | 0 |
| Pericardial effusion | 3 | 1 |
| Pulmonary hypertension | 2 | 1 |
| Headache | 33 | 1 |
| Diarrhea | 28 | 2 |
| Fatigue | 26 | 4 |
| Dyspnea | 24 | 2 |
| Musculoskeletal pain | 22 | 2 |
| Nausea | 18 | 1 |
| Skin rash[a] | 18 | 2 |
| Myalgia | 13 | 0 |
| Arthralgia | 13 | 1 |
| Infection (including bacterial, viral, fungal, and non-specified) | 13 | 1 |
| Abdominal pain | 12 | 1 |
| Hemorrhage | 12 | 1 |

**Table 4: Adverse Reactions Reported in ≥10% of Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)**

| | 100 mg Once Daily | |
|---|---|---|
| | Chronic (n=165) | |
| | All Grades | Grade 3/4 |
| **Preferred Term** | **Percent (%) of Patients** | |
| Gastrointestinal bleeding | 2 | 1 |
| Pruritus | 12 | 1 |
| Pain | 11 | 1 |
| Constipation | 10 | 1 |

[a] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 5.

**Table 5: Selected Adverse Reactions Reported in Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)[a]**

| | Minimum of 2 Years Follow-up | | Minimum of 5 Years Follow-up | | Minimum of 7 Years Follow-up | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| **Preferred Term** | **Percent (%) of Patients** | | | | | |
| Diarrhea | 27 | 2 | 28 | 2 | 28 | 2 |
| Fluid retention | 34 | 4 | 42 | 6 | 48 | 7 |
| Superficial edema | 18 | 0 | 21 | 0 | 22 | 0 |
| Pleural effusion | 18 | 2 | 24 | 4 | 28 | 5 |
| Generalized edema | 3 | 0 | 4 | 0 | 4 | 0 |
| Pericardial effusion | 2 | 1 | 2 | 1 | 3 | 1 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 2 | 1 |
| Hemorrhage | 11 | 1 | 11 | 1 | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 | 2 | 1 | 2 | 1 |

[a] Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

**Table 6: Adverse Reactions Reported in ≥10% of Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy**

| | 140 mg Once Daily | | | | | |
|---|---|---|---|---|---|---|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| **Preferred Term** | **Percent (%) of Patients** | | | | | |
| Fluid retention | 35 | 8 | 34 | 7 | 21 | 6 |
| Superficial localized edema | 18 | 1 | 14 | 0 | 3 | 0 |
| Pleural effusion | 21 | 7 | 20 | 7 | 21 | 6 |
| Generalized edema | 1 | 0 | 3 | 0 | 0 | 0 |
| Pericardial effusion | 3 | 1 | 0 | 0 | 0 | 0 |
| Congestive heart failure/cardiac dysfunction[a] | 0 | 0 | 4 | 0 | 0 | 0 |
| Pulmonary edema | 1 | 0 | 4 | 3 | 0 | 0 |
| Headache | 27 | 1 | 18 | 1 | 15 | 3 |
| Diarrhea | 31 | 3 | 20 | 5 | 18 | 0 |
| Fatigue | 19 | 2 | 20 | 1 | 9 | 3 |
| Dyspnea | 20 | 3 | 15 | 3 | 3 | 3 |
| Musculoskeletal pain | 11 | 0 | 8 | 1 | 0 | 0 |

**Table 6: Adverse Reactions Reported in ≥10% of Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy**

| | 140 mg Once Daily | | | | | |
|---|---|---|---|---|---|---|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| **Preferred Term** | Percent (%) of Patients | | | | | |
| Nausea | 19 | 1 | 23 | 1 | 21 | 3 |
| Skin rash[b] | 15 | 0 | 16 | 1 | 21 | 0 |
| Arthralgia | 10 | 0 | 5 | 1 | 0 | 0 |
| Infection (including bacterial, viral, fungal, and non-specified) | 10 | 6 | 14 | 7 | 9 | 0 |
| Hemorrhage | 26 | 8 | 19 | 9 | 24 | 9 |
| Gastrointestinal bleeding | 8 | 6 | 9 | 7 | 9 | 3 |
| CNS bleeding | 1 | 1 | 0 | 0 | 3 | 3 |
| Vomiting | 11 | 1 | 12 | 0 | 15 | 0 |
| Pyrexia | 11 | 2 | 18 | 3 | 6 | 0 |
| Febrile neutropenia | 4 | 4 | 12 | 12 | 12 | 12 |

[a] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[b] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

## Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 7 and 8). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of patients in a randomized trial of patients with newly diagnosed chronic phase CML and 5% of patients with resistance or intolerance to prior imatinib therapy *[see Warnings and Precautions (5.1)]*.

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in patients with newly diagnosed chronic phase CML are shown in Table 7. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

**Table 7: CTC Grade 3/4 Laboratory Abnormalities in Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)**

| | SPRYCEL (n=258) | Imatinib (n=258) |
|---|---|---|
| | Percent (%) of Patients | |
| **Hematology Parameters** | | |
| Neutropenia | 29 | 24 |
| Thrombocytopenia | 22 | 14 |
| Anemia | 13 | 9 |
| **Biochemistry Parameters** | | |
| Hypophosphatemia | 7 | 31 |
| Hypokalemia | 0 | 3 |
| Hypocalcemia | 4 | 3 |
| Elevated SGPT (ALT) | <1 | 2 |
| Elevated SGOT (AST) | <1 | 1 |
| Elevated Bilirubin | 1 | 0 |
| Elevated Creatinine | 1 | 1 |

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × $10^9$/L, Grade 4 <0.5 × $10^9$/L); thrombocytopenia (Grade 3 ≥25–<50 × $10^9$/L, Grade 4 <25 × $10^9$/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 8.

**Table 8: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML: Resistance or Intolerance to Prior Imatinib Therapy**

| | Chronic Phase CML 100 mg Once Daily | Advanced Phase CML 140 mg Once Daily | | |
|---|---|---|---|---|
| | (n=165) | Accelerated Phase (n=157) | Myeloid Blast Phase (n=74) | Lymphoid Blast Phase (n=33) |
| | Percent (%) of Patients | | | |
| **Hematology Parameters*** | | | | |
| Neutropenia | 36 | 58 | 77 | 79 |
| Thrombocytopenia | 24 | 63 | 78 | 85 |
| Anemia | 13 | 47 | 74 | 52 |
| **Biochemistry Parameters** | | | | |
| Hypophosphatemia | 10 | 13 | 12 | 18 |
| Hypokalemia | 2 | 7 | 11 | 15 |
| Hypocalcemia | <1 | 4 | 9 | 12 |
| Elevated SGPT (ALT) | 0 | 2 | 5 | 3 |
| Elevated SGOT (AST) | <1 | 0 | 4 | 3 |
| Elevated Bilirubin | <1 | 1 | 3 | 6 |
| Elevated Creatinine | 0 | 2 | 8 | 0 |

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × $10^9$/L, Grade 4 <0.5 × $10^9$/L); thrombocytopenia (Grade 3 ≥25–<50 × $10^9$/L, Grade 4 <25 × $10^9$/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among chronic phase CML patients with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

## 6.2 Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

A total of 135 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. Serious adverse reactions reported in ≥5% of patients

included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

### 6.3 Additional Pooled Data From Clinical Trials

The following additional adverse reactions were reported in patients in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance.

***Gastrointestinal Disorders:*** *1%–<10%* – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; *0.1%–<1%* – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; *<0.1%* – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

***General Disorders and Administration-Site Conditions:*** *≥10%* – peripheral edema, face edema; *1%–<10%* – asthenia, chest pain, chills; *0.1%–<1%* – malaise, other superficial edema; *<0.1%* – gait disturbance.

***Skin and Subcutaneous Tissue Disorders:*** *1%–<10%* – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); *0.1%–<1%* – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; *<0.1%* – leukocytoclastic vasculitis, skin fibrosis.

***Respiratory, Thoracic, and Mediastinal Disorders:*** *1%–<10%* – lung infiltration, pneumonitis, cough; *0.1%–<1%* – asthma, bronchospasm, dysphonia, pulmonary arterial hypertension; *<0.1%* – acute respiratory distress syndrome, pulmonary embolism.

***Nervous System Disorders:*** *1%–<10%* – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; *0.1%–<1%* – amnesia, tremor, syncope, balance disorder; *<0.1%* – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIth nerve paralysis, dementia, ataxia.

***Blood and Lymphatic System Disorders:*** *0.1%–<1%* – lymphadenopathy, lymphopenia; *<0.1%* – aplasia pure red cell.

***Musculoskeletal and Connective Tissue Disorders:*** *1%–<10%* – muscular weakness, musculoskeletal stiffness; *0.1%–<1%* – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis.

***Investigations:*** *1%–<10%* – weight increased, weight decreased; *0.1%–<1%* – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

***Infections and Infestations:*** *1%–<10%* – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

***Metabolism and Nutrition Disorders:*** *1%–<10%* – appetite disturbances, hyperuricemia; *0.1%–<1%* – hypoalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; *<0.1%* – diabetes mellitus.

***Cardiac Disorders:*** *1%–<10%* – arrhythmia (including tachycardia), palpitations; *0.1%–<1%* – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; *<0.1%* – cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

***Eye Disorders:*** *1%–<10%* – visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye; *0.1%–<1%* – conjunctivitis, visual impairment, photophobia, lacrimation increased.

***Vascular Disorders:*** *1%–<10%* – flushing, hypertension; *0.1%–<1%* – hypotension, thrombophlebitis, thrombosis; *<0.1%* – livedo reticularis, deep vein thrombosis, embolism.

***Psychiatric Disorders:*** *1%–<10%* – insomnia, depression; *0.1%–<1%* – anxiety, affect lability, confusional state, libido decreased.

***Pregnancy, Puerperium, and Perinatal Conditions:*** *<0.1%* – abortion.

***Reproductive System and Breast Disorders:*** *0.1%–<1%* – gynecomastia, menstrual disorder.

***Injury, Poisoning, and Procedural Complications:*** *1%–<10%* – contusion.

***Ear and Labyrinth Disorders:*** *1%–<10%* – tinnitus; *0.1%–<1%* – vertigo, hearing loss.

***Hepatobiliary Disorders:*** *0.1%–<1%* – cholestasis, cholecystitis, hepatitis.

***Renal and Urinary Disorders:*** *0.1%–<1%* – urinary frequency, renal failure, proteinuria; *<0.1%* – renal impairment.

***Immune System Disorders:*** *0.1%–<1%* – hypersensitivity (including erythema nodosum).

***Endocrine Disorders:*** *0.1%–<1%* – hypothyroidism; *<0.1%* – hyperthyroidism, thyroiditis.

## 6.4 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Infections:** hepatitis B virus reactivation

**Cardiac disorders:** atrial fibrillation/atrial flutter

**Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease

**Skin and subcutaneous tissue disorders:** Stevens-Johnson syndrome

## 7 DRUG INTERACTIONS

### 7.1 Drugs That May Increase Dasatinib Plasma Concentrations

**CYP3A4 Inhibitors:** Dasatinib is a CYP3A4 substrate. In a trial of 18 patients with solid tumors, 20-mg SPRYCEL once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib $C_{max}$ and AUC by four- and five-fold, respectively. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.1)]*.

### 7.2 Drugs That May Decrease Dasatinib Plasma Concentrations

**CYP3A4 Inducers:** When a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean $C_{max}$ and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction potential should be considered. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered *[see Dosage and Administration (2.1)]*.

**Antacids:** Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In a trial of 24 healthy subjects, administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single 50-mg dose of SPRYCEL was associated with no relevant change in dasatinib AUC; however, the dasatinib $C_{max}$ increased 26%. When 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50-mg dose of SPRYCEL, a 55% reduction in dasatinib AUC and a 58% reduction in $C_{max}$ were observed. Simultaneous administration of SPRYCEL with 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.

**$H_2$ Antagonists/Proton Pump Inhibitors:** Long-term suppression of gastric acid secretion by $H_2$ antagonists or proton pump inhibitors (e.g., famotidine and omeprazole) is likely to reduce dasatinib exposure. In a trial of 24 healthy subjects, administration of a single 50-mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and $C_{max}$ of dasatinib by 61% and 63%, respectively. In a trial of 14 healthy subjects, administration of a single 100-mg dose of SPRYCEL 22 hours following a 40-mg omeprazole dose at steady state reduced the AUC and $C_{max}$ of dasatinib by 43% and 42%, respectively. The concomitant use of $H_2$ antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids (at least 2 hours prior to or 2 hours after the dose of SPRYCEL) should be considered in place of $H_2$ antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

### 7.3 Drugs That May Have Their Plasma Concentration Altered By Dasatinib

**CYP3A4 Substrates:** Single-dose data from a trial of 54 healthy subjects indicate that the mean $C_{max}$ and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of SPRYCEL. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on limited human data, SPRYCEL can 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 dasatinib 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 *[see Warnings and Precautions (5.1, 5.3)]*.

#### Data

##### *Human Data*

Based on human experience, dasatinib is suspected to cause congenital malformations, including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy.

*Animal Data*

In nonclinical studies at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m$^2$/day] and rabbit: 0.5 mg/kg/day [6 mg/m$^2$/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng•h/mL and 44 ng•h/mL (0.1-fold the human AUC) in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, and clavicle), reduced ossification (sternum; thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia. In a pre- and postnatal development study in rats, administration of dasatinib from gestation day (GD) 16 through lactation day (LD) 20, GD 21 through LD 20, or LD 4 through LD 20 resulted in extensive pup mortality at maternal exposures that were below the exposures in patients treated with dasatinib at the recommended labeling dose.

## 8.2 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 SPRYCEL and for 2 weeks after the final dose.

## 8.3 Females and Males of Reproductive Potential

Contraception

*Females*

SPRYCEL can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraceptive methods, during treatment with SPRYCEL and for 30 days after the final dose.

Infertility

Based on animal data, dasatinib may result in damage to female and male reproductive tissues *[see Nonclinical Toxicology (13.1)]*.

## 8.4 Pediatric Use

The safety and efficacy of SPRYCEL in patients less than 18 years of age have not been established.

## 8.5 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 SPRYCEL in 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 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.

## 8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of dasatinib was evaluated in healthy volunteers with normal liver function and patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment. Compared to the healthy volunteers with normal hepatic function, the dose-normalized pharmacokinetic parameters were decreased in the patients with hepatic impairment.

No dosage adjustment is necessary in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*. Caution is recommended when administering SPRYCEL to patients with hepatic impairment.

## 8.7 Renal Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired renal function. Less than 4% of dasatinib and its metabolites are excreted via the kidney.

# 10 OVERDOSAGE

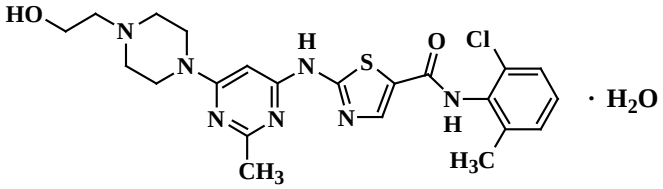
Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdosage of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*, monitor patients who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥100 mg/kg (600 mg/m$^2$) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥10 mg/kg (120 mg/m$^2$).

# 11 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-

thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:




Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

*In vitro*, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

### 12.3 Pharmacokinetics

#### Absorption

Maximum plasma concentrations ($C_{max}$) of dasatinib are observed between 0.5 and 6 hours ($T_{max}$) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 to 240 mg/day. The overall mean terminal half-life of dasatinib is 3 to 5 hours.

Data from a trial of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

#### Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active

metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100 to 500 ng/mL.

### Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

Dasatinib is a weak time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes.

### Elimination

Elimination is primarily via the feces. Following a single oral dose of [$^{14}$C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

### Effects of Age and Gender

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of dasatinib.

### Hepatic Impairment

Dasatinib doses of 50 mg and 20 mg were evaluated in eight patients with moderate (Child-Pugh class B) and seven patients with severe (Child-Pugh class C) hepatic impairment, respectively. Matched controls with normal hepatic function (n=15) were also evaluated and received a dasatinib dose of 70 mg. Compared to subjects with normal liver function, patients with moderate hepatic impairment had decreases in dose-normalized $C_{max}$ and AUC by 47% and 8%, respectively. Patients with severe hepatic impairment had dose-normalized $C_{max}$ decreased by 43% and AUC decreased by 28% compared to the normal controls.

These differences in $C_{max}$ and AUC are not clinically relevant. Dose adjustment is not necessary in patients with hepatic impairment.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

## 14 CLINICAL STUDIES

### 14.1 Newly Diagnosed Chronic Phase CML

An open-label, multicenter, international, randomized trial was conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥65 years of age, respectively. There were slightly more male than female patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39% were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%; intermediate risk: 48% and 47%; high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 9.

**Table 9: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial**

| | SPRYCEL (n=259) | | Imatinib (n=260) |
|---|---|---|---|
| **Confirmed CCyR**[a] | | | |
| **Within 12 months (95% CI)** | 76.8% (71.2–81.8) | | 66.2% (60.1–71.9) |
| **P-value** | | 0.007* | |
| **Major Molecular Response**[b] | | | |
| **12 months (95% CI)** | 52.1% (45.9–58.3) | | 33.8% (28.1–39.9) |
| **P-value** | | <0.0001 | |
| **60 months (95% CI)** | 76.4% (70.8–81.5) | | 64.2% (58.1–70.1) |

[a] Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.

[b] Major molecular response (at any time) was defined as BCR-ABL ratios ≤0.1% by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the time frame specified.

* Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance.

CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At 60 months, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast crisis while 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast crisis.

The estimated 60-month survival rates for SPRYCEL- and imatinib-treated patients were 90.9% (CI: 86.6%–93.8%) and 89.6% (CI: 85.2%–92.8%), respectively. Based on data 5 years after the last patient was enrolled in the trial, 83% and 77% of patients were known to be alive in the dasatinib and imatinib treatment groups, respectively, 10% were known to have died in both treatment groups, and 7% and 13% had unknown survival status in the dasatinib and imatinib treatment groups, 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 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).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

## 14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, 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. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

### Chronic Phase CML

*Dose-Optimization Trial:* A randomized, open-label trial was conducted in patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% CI [−6.8%–10.6%]); however, the 100-mg once-daily regimen demonstrated improved safety and tolerability.

Efficacy results are presented in Tables 10 and 11 for patients with chronic phase CML who received the recommended starting dose of 100 mg once daily.

**Table 10: Efficacy of SPRYCEL in Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML (minimum of 24 months follow-up)**

| All Patients | 100 mg Once Daily (n=167) |
|---|---|
| **Hematologic Response Rate % (95% CI)** | |
| CHR[a] | 92% (86–95) |
| **Cytogenetic Response Rate % (95% CI)** | |
| MCyR[b] | 63% (56–71) |
| CCyR | 50% (42–58) |

[a] CHR (response confirmed after 4 weeks): WBC ≤ institutional ULN, platelets <450,000/mm$^3$, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

**Table 11: Long-Term MMR of SPRYCEL in the Dose Optimization Trial: Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML[a]**

| | Minimum Follow-up Period | | |
|---|---|---|---|
| | 2 Years | 5 Years | 7 Years |
| **Major Molecular Response[b] % (n/N)** | | | |
| All Patients Randomized | 34% (57/167) | 43% (71/167) | 44% (73/167) |
| Imatinib-Resistant Patients | 33% (41/124) | 40% (50/124) | 41% (51/124) |
| Imatinib-Intolerant Patients | 37% (16/43) | 49% (21/43) | 51% (22/43) |

[a] Results reported in recommended starting dose of 100 mg once daily.

[b] Major molecular response criteria: Defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples.

Based on data 7 years after the last patient was enrolled in the trial, 44% were known to be alive, 31% were known to have died, and 25% had an unknown survival status.

By 7 years, transformation to either accelerated or blast phase occurred in nine patients on treatment in the 100 mg once-daily treatment group.

### Advanced Phase CML and Ph+ ALL

*Dose-Optimization Trial:* One randomized open-label trial was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast

phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary efficacy endpoint was MaHR. A total of 611 patients were randomized to either the SPRYCEL 140 mg once-daily or 70 mg twice-daily group. Median duration of treatment was approximately 6 months for both treatment groups. The once-daily schedule demonstrated comparable efficacy (non-inferiority) to the twice-daily schedule on the primary efficacy endpoint; however, the 140-mg once-daily regimen demonstrated improved safety and tolerability.

Response rates for patients in the 140 mg once-daily group are presented in Table 12.

**Table 12: Efficacy of SPRYCEL in Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL (2-Year Results)**

| | 140 mg Once Daily | | | |
|---|---|---|---|---|
| | **Accelerated (n=158)** | **Myeloid Blast (n=75)** | **Lymphoid Blast (n=33)** | **Ph+ ALL (n=40)** |
| **MaHR**[a] (95% CI) | 66% (59–74) | 28% (18–40) | 42% (26–61) | 38% (23–54) |
| CHR[a] (95% CI) | 47% (40–56) | 17% (10–28) | 21% (9–39) | 33% (19–49) |
| NEL[a] (95% CI) | 19% (13–26) | 11% (5–20) | 21% (9–39) | 5% (1–17) |
| **MCyR**[b] (95% CI) | 39% (31–47) | 28% (18–40) | 52% (34–69) | 70% (54–83) |
| CCyR (95% CI) | 32% (25–40) | 17% (10–28) | 39% (23–58) | 50% (34–66) |

[a] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥1000/mm$^3$, platelets ≥100,000/mm$^3$, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥500/mm$^3$ and <1000/mm$^3$, or platelets ≥20,000/mm$^3$ and ≤100,000/mm$^3$.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

CI = confidence interval ULN = upper limit of normal range.

In the SPRYCEL 140 mg once-daily group, the median time to MaHR was 1.9 months (min-max: 0.7-14.5) for patients with accelerated phase CML, 1.9 months (min-max: 0.9-6.2) for patients with myeloid blast phase CML, and 1.8 months (min-max: 0.9-2.8) for patients with lymphoid blast phase CML.

In patients with myeloid blast phase CML, the median duration of MaHR was 8.1 months (min-max: 2.7-21.1) and 9.0 (min-max: 1.8-23.1) months for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with lymphoid blast phase CML, the median duration of MaHR was 4.7 months (min-max: 3.0-9.0) and 7.9 months (min-max: 1.6-22.1) for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In

patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twice-daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 13.

**Table 13: SPRYCEL Trade Presentations**

| NDC Number | Strength | Description | Tablets per Bottle |
|---|---|---|---|
| 0003-0527-11 | 20 mg | white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “527” on the other side | 60 |
| 0003-0528-11 | 50 mg | white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “528” on the other side | 60 |
| 0003-0524-11 | 70 mg | white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “524” on the other side | 60 |
| 0003-0855-22 | 80 mg | white to off-white, biconvex, triangle, film-coated tablet with “BMS” and “80” (BMS over 80) debossed on one side and “855” on the other side | 30 |
| 0003-0852-22 | 100 mg | white to off-white, biconvex, oval, film-coated tablet with “BMS 100” debossed on one side and “852” on the other side | 30 |
| 0003-0857-22 | 140 mg | white to off-white, biconvex, round, film-coated tablet with “BMS” and “140” (BMS over 140) debossed on one side and “857” on the other side | 30 |

### 16.2 Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

### 16.3 Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.

SPRYCEL tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However, if tablets are inadvertently crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed or broken tablets.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Bleeding

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) *[see Warnings and Precautions (5.2)]*.

### Myelosuppression

Patients should be informed of the possibility of developing low blood cell counts; they should be instructed to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.1)]*.

### Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and to seek medical attention promptly if those symptoms arise *[see Warnings and Precautions (5.3)]*.

### Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during treatment with SPRYCEL and for 30 days after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

### Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

### Gastrointestinal Complaints

Patients should be informed that they may experience nausea, vomiting, or diarrhea with SPRYCEL. If these symptoms are bothersome or persistent, they should seek medical attention.

### Pain

Patients should be informed that they may experience headache or musculoskeletal pain with SPRYCEL. If these symptoms are bothersome or persistent, they should seek medical attention.

### Fatigue

Patients should be informed that they may experience fatigue with SPRYCEL. If this symptom is bothersome or persistent, they should seek medical attention.

### Rash

Patients should be informed that they may experience skin rash with SPRYCEL. If this symptom is bothersome or persistent, they should seek medical attention.

### Lactose

Patients should be informed that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

### Missed Dose

If the patient misses a dose of SPRYCEL, the patient should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

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