SPRYCEL (dasatinib) tablets, for oral use

Initial U.S. Approval: 2006

Indications and Usage (1) 11/2017
Dosage and Administration (2) 11/2017
Warnings and Precautions (5) 11/2017

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)
- pediatric patients with Ph+ CML in chronic phase (1, 14)

DOSAGE AND ADMINISTRATION

- Chronic phase CML in adults: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase Ph+ CML, or Ph+ ALL in adults: 140 mg once daily. (2)
- Chronic phase CML in pediatrics: starting dose based on body weight. (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets. (2)

DOSE FORMS AND STRENGTHS

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

CONTRAINdications

- 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. (2.5, 5.1, 5.2, 6.1)
- Fluid Retention: Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification. (2.5, 5.3, 6.1)
- Cardiac Dysfunction: Monitor patients for signs or symptoms and treat appropriately. (5.4, 6.1)
- Pulmonary Arterial Hypertension (PAH): SPRYCEL (dasatinib) 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, 6.3)
- 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)
- Effects on Growth and Development in Pediatric Patients: epiphyses delayed closure, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients. (5.10, 6.3)

ADVERSE REACTIONS

Most common adverse reactions (≥15%) in patients included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, 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

- Strong CYP3A4 Inhibitors: Dose reduction may be necessary. (2.3, 7.1)
- Strong CYP3A4 Inducers: Dose increase may be necessary. (2.3, 7.1)
- Antacids: Avoid simultaneous administration. (7.1)
- H2-Antagonists and Proton Pump Inhibitors: Avoid coadministration. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Not recommended (8.2)

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

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

10 OVERDOSE

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
2.5 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 for adult and pediatric patients are summarized in Tables 3 and 4, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

<table>
<thead>
<tr>
<th>Step</th>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ANC &lt;0.5 x 10^9/L</td>
<td>Stop SPRYCEL until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L.</td>
</tr>
<tr>
<td>2.</td>
<td>Recurrence of ANC &lt;0.5 x 10^9/L for &gt;7 days</td>
<td>Resume treatment with SPRYCEL at the original starting dose if recovery occurs in &lt;7 days.</td>
</tr>
<tr>
<td>3.</td>
<td>Platelets &lt;25 x 10^9/L or recurrence of ANC &lt;0.5 x 10^9/L for &gt;7 days</td>
<td>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).</td>
</tr>
</tbody>
</table>

*ANC*: absolute neutrophil count

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients

<table>
<thead>
<tr>
<th>Step</th>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>If cytopenia persists for more than 3 weeks</td>
<td>Reduce dose as shown in Table 2 in pediatric patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.</td>
</tr>
<tr>
<td>2.</td>
<td>If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1 x 10^9/L and platelets ≥75 x 10^9/L and resume at the original starting dose or at a reduced dose.</td>
<td>Adjust dose based on Table 2.</td>
</tr>
<tr>
<td>3.</td>
<td>If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose.</td>
<td>Adjust dose based on Table 2.</td>
</tr>
</tbody>
</table>

*ANC*: absolute neutrophil count

**Lower tablet dose not available**
For all pediatric patients, if Grade ≥3 neutropenia or thrombocytopenia recurs during complete hematologic response (CHR), interrupt SPRYCEL and resume at a reduced dose. Implement temporary dose reductions for intermediate degrees of cytopenia and disease response as needed.

Non-Hematologic Adverse Reactions
If a severe non-hematologic 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)].

2.6 Duration of Treatment
In clinical studies, treatment with SPRYCEL in adults and pediatric patients 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 and MMR-P]) has not been established.

SPRYCEL is an anion exchange product. Follow applicable special handling and disposal procedures.

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 CTCAE 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 (2.5) and Adverse Reactions (6.1)].

5.2 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 adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult 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.

5.3 Fluid Retention
SPRYCEL may cause fluid retention. After 5 years of follow-up in the adult 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 adult 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=549). In adult 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. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% 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 (2.5) and Adverse Reactions (6.1)].

5.4 Cardiovascular Events
SPRYCEL can cause cardiac dysfunction. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial in adults (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.

5.5 Pulmonary Arterial Hypertension
SPRYCEL may increase the risk of developing pulmonary arterial hypertension (PAH) in adult and pediatric patients 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
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 (6.2)].

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)].

5.10 Effects on Growth and Development in Pediatric Patients
In pediatric trials of SPRYCEL in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyseal delayed fusion, osteopenia, growth retardation, and gynecomastia [see Adverse Reactions (6.2) and Use in Specific Populations (8.4)]. Of these 5 cases, 1 case of osteopenia and 1 case of gynecomastia resolved during treatment.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Myelosuppression [see Dosage and Administration (2.5) 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)].
- Effects on growth and development in pediatric patients [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience
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 (n=2890), including 324 adult patients with newly diagnosed chronic phase CML, 2388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 97 pediatric patients with chronic phase CML. The median duration of therapy in a total of 2712 adult patients was 19.2 months (range 0 to 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 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months).

The median duration of therapy in 1094 adult patients with advanced phase CML or Ph+ ALL was 8.2 months (range 0 to 93.2 months).

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).
In the overall population of 2712 adult patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

In the randomized trial in adult patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of 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 patients with chronic phase CML, drug-related adverse reactions leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

Among the 97 pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

Adverse reactions reported in ≥10% of adult 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 5.

Adverse reactions reported in ≥10% of adult patients 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 7.

Adverse reactions reported in ≥10% of pediatric patients at a median follow-up of approximately 51.1 months are presented in Table 10.

Drug-related serious adverse reactions (SARs) were reported for 16.7% of adult 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 SARs were reported for 26.1% of patients treated at the recommended dose of 100 mg once daily in the randomized dose-optimization trial of adult patients with chronic phase CML resistant or intolerant to prior imatinib therapy. Serious adverse reactions reported in ≥5% of patients included pleural effusion (10%).

Drug-related SARs were reported for 14.4% of pediatric patients.

Chronic Myeloid Leukemia (CML)

Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of adult patients are shown in Table 5 for newly diagnosed patients with chronic phase CML and Tables 7 and 10 for CML patients with resistance or intolerance to prior imatinib therapy.

Table 5: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRYCEL (n=258)</td>
<td>SPRYCEL (n=258)</td>
<td>Imatinib (n=2)</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Superficial localized edema</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure/ cardiac dysfunction</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other bleeding</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

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 6.

Table 6: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Minimum of 1 Year Follow-up</th>
<th>Minimum of 5 Years Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Superficial localized edema</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Congestive heart failure/ cardiac dysfunction</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

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 papular, 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 7: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic (n=165)</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Superficial localized edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Infection (including bacterial, viral, fungal, and non-specified)</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

a Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash papular, 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 8.

### Table 8: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Resistant or -Intolerant Chronic Phase CML)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Minimum of 2 Years Follow-up All Grades</th>
<th>Grade 3/4</th>
<th>Minimum of 5 Years Follow-up All Grades</th>
<th>Grade 3/4</th>
<th>Minimum of 7 Years Follow-up All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>2</td>
<td>28</td>
<td>2</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>34</td>
<td>4</td>
<td>42</td>
<td>6</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>18</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>18</td>
<td>2</td>
<td>24</td>
<td>4</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>11</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

### Table 10: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients (n=97)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

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 11 and 12). 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 adult patients with newly diagnosed chronic phase CML and 5% of adult 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 SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 11. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

### Table 11: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>SPRYCEL (n=258)</th>
<th>Imatinib (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Biochemistry Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Elevated SGPT (ALT)</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Elevated LDH (AST)</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Elevated Bilirubin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated Creatinine</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 x 10^9/L, Grade 4 ≥1.0 x 10^9/L); thrombocytopenia (Grade 3 ≥50–<100 x 10^9/L, Grade 4 ≥100 x 10^9/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 ≥2.0–<3.0 mg/dL, Grade 4 ≥3.0 mg/dL); elevated bilirubin (Grade 3 ≥1–<2 mg/dL, Grade 4 ≥2 mg/dL); elevated SGPT or SGOT (Grade 3 ≥50–<100 IU/L, Grade 4 ≥100 IU/L); hypocalcemia (Grade 3 ≥<8.0 mg/dL, Grade 4 ≥8.0 mg/dL); hypophosphatemia (Grade 3 ≥<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 12.

* Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

* Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, miliaria, 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.
Table 12: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

<table>
<thead>
<tr>
<th>Hematology Parameters</th>
<th>Percent (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemistry Parameters</th>
<th>Percent (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>10</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated SGPT (ALT)</td>
<td>0</td>
</tr>
<tr>
<td>Elevated Bilirubin</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated Creatinine</td>
<td>0</td>
</tr>
</tbody>
</table>

CTC grades: neutropenia (Grade 3: ≥0.5–<1.0 × 10^9/L, Grade 4: <0.5 × 10^9/L); thrombocytopenia (Grade 3: ≥150–<450 × 10^9/L, Grade 4: <150 × 10^9/L); anemia (hemoglobin Grade 3: <90–<100 g/L, Grade 4: <90 g/L); elevated creatinine (Grade 3: 3.4–6.0 mg/dL, Grade 4: >6 mg/dL); elevated bilirubin (Grade 3: 1.0–1.5 mg/dL, Grade 4: >1.5 mg/dL); elevated SGOT (ALT) (Grade 3: 5–30 U/L, Grade 4: >30 U/L); hypocalcemia (Grade 3: <8–9 mg/dL, Grade 4: <8 mg/dL).

Among adult patients with chronic phase CML 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%).

In the pediatric studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

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%).

6.2 Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%. These adverse reactions are based on clinical relevance.

Gastrointestinal Disorders: 1%–<10% – mucosal inflammation (including mucusitis/ stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neurotoxic colitis), oral soft tissue disorder; 0.1%–<1% – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastrointestinal 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% – asthma, chest pain, chills; 0.1%–<1% – malaise, other superficial edema, peripheral swelling; <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-planar 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% – armenia, tremor, syncope, balance disorder; <0.1% – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIth nerve paralysis, dementia, ataxia.

Clinical Pharmacology:

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, tendinitis, muscle inflammation, osteonecrosis, arthritis; <0.1% – epiphyses delayed fusion (reported at 1%–<10% in the pediatric studies), growth retardation (reported at 1%–<10% in the pediatric studies).

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% – hypolipidemia, tumor lysis syndrome, dehydratation, hyperglycemia; <0.1% – diabetes mellitus.

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

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

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 liability, confusion 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.

6.3 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 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations [see Clinical Pharmacology (12.3)]. 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 [see Dosage and Administration (2.5)].

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations [see Clinical Pharmacology (12.3)]. 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.

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 H2 antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H2 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.
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 leukenopia, 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 neontates. Skeletal malformations were observed in a limited number of surviving rat and rabbit conceptions. 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% to 4% and of miscarriage is 15% to 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 leukenopia, 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•hr/mL and 44 ng•hr/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 microhepalia. 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 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, 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 97 pediatric patients with chronic phase CML were evaluated in two pediatric studies (a Phase I, open-label, non-randomized dose-ranging trial and a Phase II, open-label, non-randomized trial). Fifty-one patients (exclusively from the Phase II trial) were newly diagnosed with chronic phase CML and 46 patients (17 from the Phase I trial and 29 from the Phase II trial) were resistant or intolerant to previous treatment with imatinib. The majority of patients were treated with SPRYCEL tablets 60 mg/m^2 once daily (maximum dose of 100 mg twice daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity. The safety profile of dasatinib in pediatric subjects was comparable to that reported in studies in adult subjects with chronic phase CML. Monitor bone growth and development in pediatric patients [see Warnings and Precautions (5.10)].

8.5 Geriatric Use

No differences in confirmed Complete Cyrogentic 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 distension, diziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema, and weight decrease, and should be monitored closely.

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/atral 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-[[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyIamino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C_{30}H_{25}ClN_{5}O_{2}S-•H_{2}O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous base has a molecular weight of 488.01. Dasatinib has the following chemical structure:

[Chemical structure image]

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 hydroxypropylmelllose, 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 leukemia 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 could 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Of 2440 patients treated with SPRYCEL at all doses tested in clinical trials, 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 70 mg Bid in five Phase 2 studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7 ms to 13.4 ms.

An analysis of the data from five Phase 2 studies in patients (70 mg Bid) and a Phase 1 study in healthy subjects (100 mg single dose) suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QTc interval from baseline for subjects receiving therapeutic doses of dasatinib, with associated upper 95% confidence intervals <10 msec.

12.3 Pharmacokinetics

The pharmacokinetics of dasatinib exhibits dose proportional increases in AUC and Cmax over the dose range of 15 mg/day (0.15 times the lowest approved recommended dose) to 240 mg/day (1.7 times the highest approved recommended dose).

At 100 mg QD, the maximum concentration at steady state (C_{ss}) is 82.2 ng/mL (CV 69%), area under the plasma drug concentration time curve (AUC) is 397 ng/mL•hr (CV 55%). The clearance of dasatinib is found to be time-invariant.

Absorption

The maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 hours and 6 hours (T_{max}) following oral administration.

Food Effect

A high-fat meal increased the mean AUC of dasatinib following a single dose of 100 mg by 14%. The total calorie content of the high-fat meal was 985 kcal. The calories derived from fat, carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.
SPRYCEL® (dasatinib)

Distribution
The apparent volume of distribution is 2505 L (CV% 93%). Binding of dasatinib to human plasma proteins in vitro was approximately 96% and of its active metabolite was 93%, with no concentration dependence over the range of 100 ng/mL to 500 ng/mL. Dasatinib is a P-gp substrate in vitro.

Elimination
The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

Metabolism
Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monoxygenase 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 3% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidative metabolites.

Excretion
Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations
Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients
The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral dosages ranging from 60 mg/m² to 120 mg/m² once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m², the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) [see Dosage and Administration (2.2)]. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients <1 year old.

Patients with Hepatic Impairment
Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies
Cytochrome P450 Enzymes
The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 5-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents
The administration of a single oral dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 58% and the mean C_{max} of dasatinib by 59%.

Transporters
Dasatinib is not an inhibitor of P-gp in vitro.

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 adenomas 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 vitro 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 hyper trophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults
DASISION (Dasatinib vs Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial 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 33% 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 13.

Table 13: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

<table>
<thead>
<tr>
<th></th>
<th>SPRYCEL (n=259)</th>
<th>Imatinib (n=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed CCyR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 12 months (95% CI)</td>
<td>76.8% (71.2–81.8)</td>
<td>66.2% (60.1–71.9)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.007*</td>
<td></td>
</tr>
<tr>
<td><strong>Major Molecular Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months (95% CI)</td>
<td>52.1% (45.9–58.3)</td>
<td>33.8% (28.1–39.9)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>60 months (95% CI)</td>
<td>76.4% (70.8–81.5)</td>
<td>64.2% (58.1–70.1)</td>
</tr>
</tbody>
</table>

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

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, 53% 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 in Adults

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: 1156 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+ hematopoietic cells). 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 on-treatment 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 16.

### Dose-Optimization Trial: Adult Patients with Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL

Table 15: Long-Term MMR of SPRYCEL in the Dose Optimization Trial: Adult Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML

<table>
<thead>
<tr>
<th>Minimum Follow-up Period</th>
<th>2 Years</th>
<th>5 Years</th>
<th>7 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients Randomized</td>
<td>34% (57/167)</td>
<td>43% (71/167)</td>
<td>44% (73/167)</td>
</tr>
<tr>
<td>Imatinib-Resistant Patients</td>
<td>33% (41/124)</td>
<td>40% (50/124)</td>
<td>41% (51/124)</td>
</tr>
<tr>
<td>Imatinib-Intolerant Patients</td>
<td>37% (16/43)</td>
<td>49% (21/43)</td>
<td>51% (22/43)</td>
</tr>
</tbody>
</table>

Table 16: Efficacy of SPRYCEL in Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL (2-Year Results)

<table>
<thead>
<tr>
<th>Ph+ ALL</th>
<th>(n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRa</td>
<td>66% (95% CI) (59–74) (18–40) (26–61) (23–54)</td>
</tr>
<tr>
<td>CHRb</td>
<td>47% (95% CI) (40–56) (10–28) (9–39) (19–49)</td>
</tr>
<tr>
<td>NELc</td>
<td>19% (95% CI) (13–26) (5–20) (9–39) (1–17)</td>
</tr>
<tr>
<td>MCRyb</td>
<td>39% (95% CI) (31–47) (18–40) (34–69) (54–83)</td>
</tr>
<tr>
<td>CCyRd</td>
<td>32% (95% CI) (25–40) (10–28) (23–58) (34–66)</td>
</tr>
</tbody>
</table>

**Notes:**

a Hematologic response criteria (all responses confirmed after 4 weeks); Major hematologic response (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

b CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus promyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

c NEL-same criteria as for CHR but ANC >500/mm^3 and <1000/mm^3, or platelets >200,000/mm^3 and <1,000,000/mm^3.

d MCRy combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.
14.3 CML in Pediatric Patients

The efficacy of SPRYCEL in pediatric patients was evaluated in two pediatric studies of 97 patients with chronic phase CML. Among 97 patients with chronic phase CML treated in two pediatric studies, an open-label, non-randomized dose-ranging trial (NCT00360202) and an open-label, non-randomized, single-arm trial (NCT00777036), 51 patients (exclusively from the single-arm trial) had newly diagnosed with chronic phase CML and 46 patients (17 from the dose-ranging trial and 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 pediatric patients were treated with SPRYCEL tablets 60 mg/m² once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Baseline demographic characteristics of the 46 imatinib resistant or intolerant patients were: median age 13.5 years (range 2 to 20 years), 78.3% White, 15.2% Asian, 4.4% Black, 2.2% other, and 52% female. Baseline characteristics of the 51 newly diagnosed patients were: median age 12.8 years (range 1.9 to 17.8 years), 60.8% White, 31.4% Asian, 5.9% Black, 2% Other, and 49% female.

Median duration of follow-up was 5.2 years (range 0.5 to 9.3 years) for the imatinib resistant or intolerant patients and 4.5 years (range 1.3 to 6.4 years) for the newly diagnosed patients, respectively. Efficacy results for the two pediatric studies are summarized in Table 17.

Table 17 shows increasing trend for response for CCyR, MCyR, and MMR across time (3 months to 24 months). The increasing trend in response for all three endpoints is seen in both the newly diagnosed and imatinib resistant or intolerant patients.

### Table 17: Efficacy of SPRYCEL in Pediatric Patients with CP-CML Cumulative Response Over Time by Minimum Follow-Up Period

<table>
<thead>
<tr>
<th>Response</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCyR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>43.1%</td>
<td>66.7%</td>
<td>96.1%</td>
<td>96.1%</td>
</tr>
<tr>
<td>(N=51)</td>
<td>(29.3, 57.8)</td>
<td>(52.1, 79.2)</td>
<td>(86.5, 99.5)</td>
<td>(86.5, 99.5)</td>
</tr>
<tr>
<td>Prior imatinib</td>
<td>45.7%</td>
<td>71.7%</td>
<td>78.3%</td>
<td>82.6%</td>
</tr>
<tr>
<td>(N=46)</td>
<td>(30.9, 61.0)</td>
<td>(56.5, 84.0)</td>
<td>(63.6, 89.1)</td>
<td>(68.6, 92.2)</td>
</tr>
<tr>
<td>MCyR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>60.8%</td>
<td>90.2%</td>
<td>98.0%</td>
<td>98.0%</td>
</tr>
<tr>
<td>(N=51)</td>
<td>(46.1, 74.2)</td>
<td>(78.6, 96.7)</td>
<td>(89.6, 100)</td>
<td>(89.6, 100)</td>
</tr>
<tr>
<td>Prior imatinib</td>
<td>60.9%</td>
<td>82.6%</td>
<td>89.1%</td>
<td>89.1%</td>
</tr>
<tr>
<td>(N=46)</td>
<td>(45.4, 74.9)</td>
<td>(68.6, 92.2)</td>
<td>(76.4, 96.4)</td>
<td>(76.4, 96.4)</td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>7.8%</td>
<td>31.4%</td>
<td>56.9%</td>
<td>74.5%</td>
</tr>
<tr>
<td>(N=51)</td>
<td>(2.2, 18.9)</td>
<td>(13.1, 45.9)</td>
<td>(42.2, 70.7)</td>
<td>(60.4, 85.7)</td>
</tr>
<tr>
<td>Prior imatinib</td>
<td>15.2%</td>
<td>26.1%</td>
<td>39.1%</td>
<td>52.2%</td>
</tr>
<tr>
<td>(N=46)</td>
<td>(6.3, 28.9)</td>
<td>(14.3, 41.1)</td>
<td>(25.1, 54.6)</td>
<td>(36.9, 67.1)</td>
</tr>
</tbody>
</table>

*Patients from pediatric study of newly diagnosed CP-CML receiving oral tablet formulation

With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, MMR could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.5+ to 66.5+ months for CCyR, (1.4 to 66.5+ months for MCyR), and (5.4+ to 72.5+ months for subjects who achieved MMR by month 24 and 0.3+ to 72.5+ months for subjects who achieved MMR at any time), where ‘+’ indicates a censored observation.

With a median follow-up of 5.2 years in imatinib resistant or - intolerant patients, the median durations of CCyR, MCyR, and MMR could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.4 to 66.9+ months for CCyR, (2.4 to 86.9+ months for MCyR, and (2.6+ to 73.6+ months for MMR), where ‘+’ indicates a censored observation.

The median time to response for MCyR was 2.9 months (95% CI: 2.8 months, 3.5 months) in the pooled imatinib-resistant/imatinib intolerant CP-CML patients. The median time to response for CCyR was 3.3 months (95% CI: 2.8 months, 4.7 months) in the pooled imatinib-resistant/imatinib intolerant CP-CML patients. The median time to response for MMR was 8.3 months (95% CI: 5.0 months, 11.8 months) in the pooled imatinib-resistant/imatinib intolerant CP-CML patients.

In the Phase II pediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or -intolerant patients progressed to blast phase CML.
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.

- Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart [see Drug Interactions (7.1)].

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.
**What is SPRYCEL?**

SPRYCEL® is a prescription medicine used to treat:
- adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment, including Gleevec® (imatinib mesylate).
- adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment.
- children with Ph+ CML in chronic phase.

**Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:**
- have problems with your immune system
- have heart problems, including a condition called congenital long QT syndrome
- have low potassium or low magnesium levels in your blood
- are lactose (milk sugar) intolerant
- are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment and for 30 days after your final dose of SPRYCEL. Talk to your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with SPRYCEL.
- are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your final dose of SPRYCEL.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.

**How should I take SPRYCEL?**
- Take SPRYCEL exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider.
- Take SPRYCEL one (1) time a day.
- Take SPRYCEL with or without food, either in the morning or in the evening.
- Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets.
- You should not drink grapefruit juice during treatment with SPRYCEL.
- If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time.
If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of SPRYCEL?

SPRYCEL may cause serious side effects, including:

- **Low blood cell counts.** Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
  - unusual bleeding or bruising of your skin
  - bright red or dark tar-like stools
  - decreased alertness, headache, or change in speech

- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
  - swelling all over your body
  - weight gain
  - shortness of breath, especially if this happens with low levels of physical activity or at rest
  - dry cough
  - chest pain when taking a deep breath

- **Heart problems.** SPRYCEL may cause an abnormal heart rate, heart problems, or a heart attack. Your healthcare provider will monitor the potassium and magnesium levels in your blood, and your heart function.

- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).

- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.

- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS.

- **Slowing of growth and development in children.** Effects on bone growth and development in children with chronic phase CML have happened with SPRYCEL and can sometimes be severe.

The most common side effects of SPRYCEL in adults include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain
The most common side effects of SPRYCEL in children include:

- headache
- nausea
- pain in hands or feet (extremities)
- diarrhea
- skin rash
- stomach (abdomen) pain

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

For more information, go to www.sprycel.com or call 1-800-332-2056.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: November 2017

729US1704465-01-01

Bristol-Myers Squibb