

## Data Sheet

### Name Of Medicine

**Sprycel® (Dasatinib) Tablets**

### Presentation

**SPRYCEL® (dasatinib)** tablets are available as film-coated, white to off-white, biconvex, round tablets with “BMS” debossed on one side and “527” (20mg), or “524” (70mg) on the other side.

The 50mg tablets are oval shaped debossed “BMS” on one side and “528” on the other side.

The 100 mg tablets are oval shaped debossed “BMS 100” on one side and “852” on the other side.

**SPRYCEL®** film coated tablets contain the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating contains: hypromellose, titanium dioxide, and polyethylene glycol.

### Uses

#### MECHANISM of ACTION

**Dasatinib** inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nanomolar or subnanomolar concentrations. **Dasatinib** also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of kinase’s active conformation.

**Dasatinib** has been demonstrated to inhibit the survival/proliferation of human leukaemic cell lines in vitro, and to inhibit the growth of human CML (chronic myeloid leukaemia) xenografts in SCID mice, in both imatinib-sensitive and resistant models of the disease. Antileukaemic activity was seen in **dasatinib**-treated mice in a model of CML with CNS involvement. Nonclinical studies show that **dasatinib** can overcome imatinib resistance resulting from BCR-ABL independence, most BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving SRC-family kinases (LYN and FYN) and P-glycoprotein (multi-drug resistance protein 1) overexpression.

#### PHARMACOKINETICS

The pharmacokinetics of **SPRYCEL® (dasatinib)** were evaluated in 229

healthy subjects and in 84 patients with leukaemia.

## Absorption

**Dasatinib** is rapidly absorbed in patients following oral administration. The absolute bioavailability of **dasatinib** has not been determined. Peak concentrations were observed between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUC<sub>0-∞</sub>) is approximately proportional to the dose increment across doses ranging from 25mg to 120mg twice daily (BID).

Data from a study of 54 healthy subjects administered a single, 100mg dose of **dasatinib** 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of **dasatinib**. Consumption of a low-fat meal 30 minutes prior to **dasatinib** resulted in a 21% increase in the mean AUC of **dasatinib**. The observed food effects are unlikely to be clinically significant.

## Distribution

In patients, **SPRYCEL**<sup>®</sup> has a large apparent volume of distribution (2505 L) suggesting that the drug is extensively distributed in the extravascular space.

## Metabolism

**Dasatinib** is extensively metabolized in humans. In a study of 8 healthy subjects administered 100mg of [<sup>14</sup>C]-labelled **dasatinib**, unchanged **dasatinib** represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of **dasatinib** are unlikely to play a major role in the observed pharmacology of the drug. The overall mean terminal half-life of **dasatinib** is approximately 5-6 hours. CYP3A4 is a major enzyme responsible for the metabolism of **dasatinib**.

## Elimination

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [<sup>14</sup>C]-labelled **dasatinib**, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the administered radioactivity recovered in the urine and faeces, respectively. Unchanged **dasatinib** accounted for 0.1% and 19% of the administered dose in urine and faeces, respectively, with the remainder of the dose being metabolites.

## Special Populations

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of **SPRYCEL**<sup>®</sup>.

The pharmacokinetics of **SPRYCEL**<sup>®</sup> have not been evaluated in paediatric patients.

The pharmacokinetics of **SPRYCEL**<sup>®</sup> in patients with renal impairment have not been determined.

The effect of hepatic impairment on the single-dose pharmacokinetics of

**dasatinib** was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic-impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of **dasatinib**. The mean  $C_{max}$  and AUC of **dasatinib** adjusted for the 70 mg dose was decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean  $C_{max}$  and AUC adjusted for the 70 mg dose was decreased by 43% and 28% respectively, compared to subjects with normal hepatic function. (see **Warnings And Precautions**)

## Indications

**SPRYCEL**<sup>®</sup> (**dasatinib**) is indicated for the treatment of adults aged 18 years or over with newly diagnosed chronic myeloid leukaemia (CML).

**SPRYCEL**<sup>®</sup> (**dasatinib**) is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.

**SPRYCEL**<sup>®</sup> is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

## DOSAGE AND ADMINISTRATION

The recommended starting dosage of **SPRYCEL**<sup>®</sup> (**dasatinib**) for chronic phase CML is 100mg administered orally once daily (QD). The recommended starting dosage of **SPRYCEL**<sup>®</sup> for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140mg/day administered orally once daily, and should be taken consistently either in the morning or the evening.

In clinical studies, treatment with **SPRYCEL**<sup>®</sup> was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a CCyR has not been investigated.

To achieve the recommended dose, **SPRYCEL**<sup>®</sup> is available as 20 mg, 50 mg, 70 mg and 100 mg film-coated tablets. Dose increase or reduction is recommended based on patient response and tolerability.

### Dose escalation

In clinical studies in adult CML and Ph+ ALL patients, dose escalation to 140mg 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 haematologic or cytogenetic response at the recommended starting dosage.

### Dose adjustment for adverse reactions

#### *Myelosuppression*

In clinical studies, myelosuppression was managed by dose interruption, dose

reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 1.

<b>Table 1</b>		<b>Dose Adjustments for Neutropenia and Thrombocytopenia</b>
Chronic Phase CML (starting dose 100mg once daily)	ANC* $<0.5 \times 10^9/L$ and/or Platelets $<50 \times 10^9/L$	<ol style="list-style-type: none"> <li>1. Stop <b>SPRYCEL</b><sup>®</sup> until ANC <math>\geq 1.0 \times 10^9/L</math> and platelets <math>\geq 50 \times 10^9/L</math></li> <li>2. Resume treatment with <b>SPRYCEL</b><sup>®</sup> at the original starting dose</li> <li>3. If platelets <math>&lt;25 \times 10^9/L</math> and/or recurrence of ANC <math>&lt;0.5 \times 10^9/L</math> for <math>&gt;7</math> days, repeat step 1 and resume <b>SPRYCEL</b><sup>®</sup> at a reduced dose of 80mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).</li> </ol>
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* $<0.5 \times 10^9/L$ and/or Platelets $<10 \times 10^9/L$	<ol style="list-style-type: none"> <li>1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy)</li> <li>2. If cytopenia is unrelated to leukaemia, stop <b>SPRYCEL</b><sup>®</sup> until ANC <math>\geq 1.0 \times 10^9/L</math> and platelets <math>\geq 20 \times 10^9/L</math> and resume at the original starting dose</li> <li>3. If recurrence of cytopenia, repeat step 1 and resume <b>SPRYCEL</b><sup>®</sup> at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode)</li> <li>4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily.</li> </ol>
*ANC: absolute neutrophil count		

## Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with **SPRYCEL**<sup>®</sup> 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 initial severity of the event.

Paediatric population: The safety and efficacy of **SPRYCEL**<sup>®</sup> in children and adolescents below 18 years of age have not yet been established. No data are available (see **Warnings And Precautions**).

Elderly population: No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in the elderly (see **Warnings And Precautions**).

Hepatic impairment: Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, caution is recommended when **SPRYCEL**<sup>®</sup> is administered to patients with hepatic impairment. (see **Warnings And Precautions**).

Renal impairment: Since the renal clearance of **dasatinib** and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency (see **Warnings And Precautions**).

Method of Administration: To be administered orally. Tablets must not be crushed or cut in order to minimize risk of dermal exposure, they must be swallowed whole. **SPRYCEL**<sup>®</sup> can be taken with or without a meal and should be taken consistently either in the morning or the evening.

## Overdosage

Experience with overdose of **SPRYCEL**<sup>®</sup> in clinical studies is limited to isolated cases. Overdosage of 280mg per day for one week was reported in 2 patients and both developed a significant decrease in platelet count. Since **SPRYCEL**<sup>®</sup> is associated with severe myelosuppression, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

## Preparation and Administration Precautions

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**SPRYCEL**<sup>®</sup> (**dasatinib**) 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 and/or broken tablets.

## Contraindications

Use of **SPRYCEL**<sup>®</sup> is contraindicated in patients with hypersensitivity to **dasatinib** or to any other component of **SPRYCEL**<sup>®</sup>.

## Warnings And Precautions

### General

#### Myelosuppression

Treatment with **SPRYCEL**<sup>®</sup> is associated with thrombocytopenia, neutropenia and anaemia. Their occurrence is more frequent in patients with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding **SPRYCEL**<sup>®</sup> temporarily or dose reduction (see **DOSAGE and ADMINISTRATION** and **ADVERSE REACTIONS: Laboratory Abnormalities**). CTC Grade 3 or 4 (severe) cases of anaemia were managed with blood transfusions.

In a Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with **SPRYCEL**<sup>®</sup> 100mg once daily than in patients treated with **SPRYCEL**<sup>®</sup> 70mg twice daily.

#### Bleeding Related Events

In the Phase III study in patients with newly diagnosed chronic phase CML, 1 patient (< 1%) receiving **SPRYCEL**<sup>®</sup> compared to 2 patients (1%) receiving imatinib had Grade 3 or 4 haemorrhage. In clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe CNS haemorrhage, including fatalities, occurred in <1% of patients receiving **SPRYCEL**<sup>®</sup>. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4% of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruptions and transfusions. Other cases of Grade 3 or 4 haemorrhage occurred in 2% of patients with resistance or intolerance to prior imatinib therapy. Most bleeding events in these patients were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that **SPRYCEL**<sup>®</sup> treatment reversibly affects platelet activation.

Patients were excluded from participation in initial imatinib-resistant **SPRYCEL**<sup>®</sup> (**dasatinib**) clinical studies if they took medications that inhibit platelet function or anticoagulants.

In subsequent trials, the use of anticoagulants, acetylsalicylic acid, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with **SPRYCEL**<sup>®</sup> if the platelet count was > 50 – 75 x 10<sup>9</sup>/L. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

## Fluid Retention

**SPRYCEL**<sup>®</sup> is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, Grade 3 or 4 fluid retention was reported in 2 patients (1%) in each of the **dasatinib** and the imatinib-treatment groups (**ADVERSE REACTIONS**). In clinical studies in patients with resistance or intolerance to prior imatinib therapy, Grade 3 or 4, fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients respectively. Severe congestive heart failure/cardiac dysfunction was reported in 2% patients. In these studies, Grade 3 or 4 ascites and generalised oedema were each reported in <1% of patients and Grade 3 or 4 pulmonary oedema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require oxygen therapy and thoracentesis. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

In the Phase III dose-optimization studies, fluid retention events were reported less frequently in patients treated with **SPRYCEL**<sup>®</sup> once daily than in patients treated with **SPRYCEL**<sup>®</sup> twice daily

## QT Prolongation

*In vitro* data showing inhibition of the hERG K<sup>+</sup> channel expressed in mammalian cells and action potential prolongation in rabbit Purkinje fibres by **dasatinib** and a number of its metabolites suggest that **dasatinib** has the potential to prolong cardiac ventricular repolarisation (QT interval).

In 258 **SPRYCEL**<sup>®</sup>-treated patients and 258 imatinib-treated patients in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each group had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3.0 msec in **SPRYCEL**<sup>®</sup>-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1%) in each group experienced a QTcF > 500 msec. In phase II, single-arm clinical studies in 865 patients with leukaemia treated with **SPRYCEL**<sup>®</sup> the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4-6 msec; the upper 95% confidence intervals for all mean changes from baseline were <7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy treated with **SPRYCEL**<sup>®</sup>, 14 (<1%) had QT prolongation reported as an adverse reaction. Twenty-one (21) of these patients (1%) experienced a QTcF >500 msec.

**SPRYCEL**<sup>®</sup> should be administered with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products which lead to QT prolongation and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to **SPRYCEL**<sup>®</sup> administration.

## Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterization, has been reported in association with SPRYCEL<sup>®</sup> treatment in post-marketing reports. In these cases, PAH was reported after initiation of SPRYCEL<sup>®</sup> therapy, including after more than one year of treatment. Patients with PAH reported during SPRYCEL<sup>®</sup> treatment were often taking concomitant medications or had comorbidities in addition to the underlying malignancy.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL<sup>®</sup> therapy. Patients who develop dyspnea and fatigue after initiation of therapy should be evaluated for more common etiologies including pleural effusion, pulmonary edema, anemia, or lung infiltration. During this evaluation, guidelines for non-hematologic adverse reactions should be followed (see DOSAGE AND ADMINISTRATION): if the adverse reaction is severe, treatment must be withheld until the event has resolved or improved. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, SPRYCEL<sup>®</sup> should be permanently discontinued. Follow up should be performed according to standard practice guidelines. Improvements in hemodynamic and clinical parameters have been observed in SPRYCEL<sup>®</sup> treated patients with PAH following cessation of SPRYCEL<sup>®</sup> therapy.

## Cardiac Adverse Reactions

**SPRYCEL<sup>®</sup>** was studied in a randomised trial of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction and fatal myocardial infarction were reported in patients taking **SPRYCEL<sup>®</sup>**. Adverse cardiac events were more frequent in patients with risk factors or a previous medical history of cardiac disease. Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see ADVERSE REACTIONS).

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

## Lactose Content

**SPRYCEL<sup>®</sup>** contains 135mg lactose in a 100mg daily dose and 189mg of lactose in a 140mg daily dose.

## Hepatic Impairment

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. Due to the limitations of this clinical study, caution is recommended when **SPRYCEL<sup>®</sup>** is administered to patients with hepatic impairment.

## Renal Impairment

There are currently no clinical studies with **SPRYCEL**<sup>®</sup> in patients with impaired renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine concentration >3 times the upper limit of normal range, and clinical studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range).

**Dasatinib** and its metabolites are minimally excreted via the kidney. Since the renal excretion of unchanged **dasatinib** and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

### Carcinogenicity

Dasatinib was not carcinogenic in rats at doses up to 3 mg/kg/day, a dose which gave rise to a dasatinib plasma exposure level close to what is observed clinically

### Genotoxicity

**Dasatinib** was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not clastogenic in an *in vivo* rat micronucleus study. Clastogenicity was observed with **dasatinib** *in vitro* in assays with Chinese hamster ovary cells in the absence and presence of metabolic activation.

### Effects on Fertility

**Dasatinib** caused atrophy/degeneration of the testis in rats and monkeys and an increase in the number of corpora lutea in the ovaries in rats at doses producing plasma exposure levels below or close to that anticipated in patients receiving **SPRYCEL**<sup>®</sup> therapy.

**Dasatinib** did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryoletality at dose levels approximating human clinical exposures. In embryofetal development studies, dasatinib likewise induced embryoletality with associated decreases in litter size in rats as well as fetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis.

## Pregnancy

### Pregnancy Category D

**Dasatinib** may cause foetal harm when administered to a pregnant woman. In nonclinical studies, at exposure levels that are readily achievable in humans receiving therapeutic doses of **SPRYCEL**<sup>®</sup> serious embryo foetal toxicity was observed in both pregnant rats and rabbits. Malformations and foetal death were observed in rats treated with **dasatinib**.

**SPRYCEL**<sup>®</sup> is therefore not recommended for use in women who are pregnant or contemplating pregnancy. Women must be advised to avoid becoming pregnant while on therapy. If **SPRYCEL**<sup>®</sup> is used during pregnancy, or if the patient becomes pregnant while taking **SPRYCEL**<sup>®</sup> the patient should be apprised of the potential hazard to the foetus.

The potential effects of **SPRYCEL**<sup>®</sup> on sperm have not been studied. Sexually active male patients taking **SPRYCEL**<sup>®</sup> should use adequate contraception.

### **Use in Lactation**

It is unknown whether **SPRYCEL**<sup>®</sup> is excreted in human milk. Women who are taking **SPRYCEL**<sup>®</sup> should not breastfeed.

### **Paediatric Use**

The safety and efficacy of **SPRYCEL**<sup>®</sup> in patients <18 years of age have not been established.

### **Geriatric Use**

In the newly diagnosed chronic phase CML study, 25 patients (10%) were 65 years of age and older and 7 patients (3%) were 75 years of age and older. Of the 2182 patients in clinical studies of **SPRYCEL**<sup>®</sup> with resistance or intolerance to prior imatinib therapy, 547 (25%) were 65 years of age and older and 105 (5%) were 75 years of age and older. While the safety profile of **SPRYCEL**<sup>®</sup> in the geriatric population is similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention events and dyspnea and should be monitored closely. No differences in efficacy were observed between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and older.

## **Interactions**

### **Interactions with Other Medicines**

*Drugs that may increase **dasatinib** plasma concentrations*

CYP3A4 Inhibitors: In vitro, **dasatinib** is a CYP3A4 substrate. Concomitant use of **SPRYCEL**<sup>®</sup> and substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, sequinavir, telithromycin, lopinavir, grapefruit juice) may increase exposure to **dasatinib**. Therefore, in patients receiving treatment with **SPRYCEL**<sup>®</sup>, systemic administration of a potent CYP3A4 inhibitor is not recommended. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity.

*Drugs that may decrease **dasatinib** plasma concentrations*

**CYP3A4 Inducers:** Drugs that induce CYP3A4 activity may increase metabolism and decrease **dasatinib** plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) with **SPRYCEL**<sup>®</sup> is not recommended. In healthy subjects, the concomitant use of **SPRYCEL**<sup>®</sup> and rifampicin, a potent CYP3A4 inducer, resulted in a five-fold decrease in **dasatinib** exposure. In patients for whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used.

**Antacids:** Nonclinical data demonstrate that the solubility of **dasatinib** is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with **SPRYCEL**<sup>®</sup> reduced the AUC of a single dose of **SPRYCEL**<sup>®</sup> by 55% and the C<sub>max</sub> by 58%. However, when antacids were administered 2 hours prior to a single dose of **SPRYCEL**<sup>®</sup>, no relevant changes in **SPRYCEL**<sup>®</sup> concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following **SPRYCEL**<sup>®</sup>. Simultaneous administration of **SPRYCEL**<sup>®</sup> with antacids should be avoided.

**Histamine-2 Antagonists/Proton Pump Inhibitors:** Long-term suppression of gastric secretion by histamine-2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce **dasatinib** exposure. In a study of 14 healthy subjects, administration of a single 100 mg dose of **SPRYCEL**<sup>®</sup> 22 hours following a 4 day, 40 mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C<sub>max</sub> of dasatinib by 42%. The concomitant use of histamine-2 antagonists or proton pump inhibitors with **SPRYCEL**<sup>®</sup> is not recommended. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of **SPRYCEL**<sup>®</sup> reduced **dasatinib** exposure by 61%. The use of antacids (at least 2 hours prior to or 2 hours after the dose of **SPRYCEL**<sup>®</sup> should be considered in place of histamine-2 antagonists or proton pump inhibitors in patients receiving **SPRYCEL**<sup>®</sup> therapy.

*Drugs that may have their plasma concentration altered by **dasatinib***

**CYP3A4 Substrates:** Dasatinib is an inhibitor of CYP3A4. In a study in healthy subjects, a single 100mg dose of **SPRYCEL**<sup>®</sup> increased exposure to simvastatin, a known CYP3A4 substrate, by 20%. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporin, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving **SPRYCEL**<sup>®</sup> (See **PHARMACOLOGY**).

In vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

## ADVERSE REACTIONS

The data described below reflect exposure to **SPRYCEL**<sup>®</sup> in 2,440 patients in clinical trials, including 258 patients with newly diagnosed chronic phase CML with a minimum of 12 months follow-up (starting dose 100 mg once daily) and 2,182 patients with imatinib resistant or intolerant CML or Ph+ALL with a minimum of 24 months follow-up (starting dosage 100mg once daily, 140mg once daily, 50mg twice daily, or 70mg twice daily). The median duration of therapy for patients with resistance or intolerance to imatinib was 15 months (range <1-36 months). Of the 2,440 patients treated, 23% were ≥65 years of age, while 5% were ≥75 years of age.

In the Phase III study of patients with newly diagnosed chronic phase CML the median duration of therapy was 14 months (range 0.03 – 24 months) for **SPRYCEL**<sup>®</sup> and 14 months (range 0.3 – 26 months) for imatinib; the median average daily dose was 99 mg and 400 mg, respectively.

The majority of **SPRYCEL**<sup>®</sup>-treated patients experienced adverse reactions at some time, regardless of dose or schedule. Most reactions were of mild-to-moderate grade.

In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for adverse reactions in 5% of **SPRYCEL**<sup>®</sup>-treated patients and 4% of imatinib-treated patients. Among patients with resistance or intolerance to imatinib therapy, the rates of discontinuation for adverse reactions were 15% in chronic phase CML, 16% in accelerated phase CML, 15% in myeloid blast phase CML, 8% in lymphoid blast phase CML and 8% in Ph+ ALL. In the Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, the rate of discontinuation for adverse drug reaction was lower for patients treated with 100mg once daily than for those treated with 70mg twice daily (10% and 16%, respectively).

Less frequent dose reductions and interruptions were also reported for patients with advanced phase CML and Ph+ALL treated with 140 mg once daily than for those treated with 70 mg twice daily.

The majority of imatinib-intolerant patients in chronic phase CML were able to tolerate treatment with **dasatinib**. In clinical studies in chronic phase CML, 10 of the 215 imatinib-intolerant patients had the same Grade 3 or 4 non-haematological toxicity with **SPRYCEL**<sup>®</sup>, as they did with prior imatinib; 8 of the 10 patients were managed with dose reduction and were able to continue **SPRYCEL**<sup>®</sup> treatment.

The most frequently reported adverse reactions reported in **SPRYCEL**<sup>®</sup>-treated patients with newly diagnosed chronic phase CML were fluid retention (including pleural effusion), diarrhoea, headache, rash and musculoskeletal pain. The most frequently reported adverse reactions in **SPRYCEL**<sup>®</sup>-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, skin rash, headache, haemorrhage, fatigue, nausea, dyspnoea, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of **SPRYCEL**<sup>®</sup>-treated patients with resistance or intolerance to prior imatinib therapy.

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”.

In the newly diagnosed chronic phase CML study, Grade 1 and 2 pleural effusion were reported in 26 patients (10%) receiving **SPRYCEL**<sup>®</sup> (see Table 2). The median time to onset was 28 weeks (range 4-88 weeks). This reaction was usually reversible and managed by interrupting **SPRYCEL**<sup>®</sup> treatment and using diuretics or other appropriate supportive care measure (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**). With appropriate medical care, 23 patients (88% of those with pleural effusion) were able to continue on **SPRYCEL**<sup>®</sup>.

The use of **SPRYCEL**<sup>®</sup> is associated with fluid retention with Grade 3 and 4 cases in 10% of patients with resistance or intolerance to prior imatinib therapy. Grade 3 or 4 pleural and pericardial effusion were reported in 7% and 1% of patients, respectively. Severe congestive heart failure/cardiac dysfunction was reported in 2% of patients. Grade 3 or 4 ascites and generalised oedema were each reported in < 1%. One percent of patients experienced severe pulmonary oedema. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

Bleeding drug-related events, ranging from petechiae and epistaxis to Grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking **SPRYCEL**<sup>®</sup>. In the Phase III study in patients with newly diagnosed chronic phase CML, 1 patient (< 1%) receiving **SPRYCEL**<sup>®</sup> compared to 2 patients (1%) receiving imatinib had Grade 3 or 4 haemorrhage. In clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe CNS haemorrhage occurred in < 1% of patients; 8 cases were fatal and 6 of them were associated with CTC Grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4% of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruption and transfusions. Other Grade 3 or 4 haemorrhage occurred in 2% of patients with resistance or intolerance to prior imatinib therapy. Most bleeding related events in these patients were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that **SPRYCEL**<sup>®</sup> treatment reversibly affects platelet activation.

Treatment with **SPRYCEL**<sup>®</sup> is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML.

QT Prolongation: in the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1%) of the **SPRYCEL**<sup>®</sup>-treated patients, and one patient (< 1%) of the imatinib-treated patients had a QTcF > 500 msec (see **PRECAUTIONS**).

In 5 Phase II clinical studies in patients with resistance or intolerance to prior imatinib therapy, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving **SPRYCEL**<sup>®</sup> 70 mg twice daily. QT interval was corrected for heart rate by Fridericia's method.

At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4 – 6 msec, with associated upper 95% confidence intervals < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received **SPRYCEL**<sup>®</sup> in clinical studies, 14 (< 1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF > 500 msec (see **WARNINGS AND PRECAUTIONS**).

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see **WARNINGS AND PRECAUTIONS**).

In clinical trials with patients with resistance or intolerance to prior imatinib therapy, it was recommended that treatment with imatinib be discontinued at least 7 days before starting treatment with **SPRYCEL**<sup>®</sup>.

The comparative frequency of adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of the patients with newly diagnosed chronic phase CML are presented in Table 2.

**Table 2: Adverse Reactions Reported in  $\geq 10\%$  of Patients with Newly Diagnosed Chronic Phase CML**

Preferred Term	All Grades		Grade 3/4	
	SPRYCEL <sup>®</sup> n= 258	imatinib n= 258	SPRYCEL <sup>®</sup> n= 258	imatinib n= 258
	Percent (%) of Patients			
<b>Fluid Retention</b>	19	42	1	1
Superficial localised oedema	9	36	0	< 1
Pleural effusion	10	0	0	0
Generalised oedema	2	6	0	0
Pericardial effusion	1	< 1	< 1	0
Congestive heart failure/ cardiac dysfunction <sup>a</sup>	2	1	< 1	< 1
Pulmonary hypertension	1	0	0	0
Pulmonary oedema	< 1	0	0	0
Diarrhoea	17	17	< 1	1
Nausea	8	20	0	0
Vomiting	5	10	0	0
Headache	12	10	0	0
Rash <sup>b</sup>	11	17	0	1
Fatigue	8	10	< 1	0
Musculoskeletal pain	11	14	0	< 1
Myalgia	6	12	0	0
Muscle inflammation	4	17	0	< 1
<b>Haemorrhage<sup>c</sup></b>	5	5	< 1	1
Gastrointestinal bleeding	1	< 1	< 1	0
Other bleeding <sup>d</sup>	4	4	0	1

<sup>a</sup> Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.

<sup>b</sup> Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.

<sup>c</sup> Important adverse reaction of special interest with < 10% frequency.

<sup>d</sup> Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

In the Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy (median duration of treatment approximately 23 months), the incidence of pleural effusion and congestive heart failure/cardiac dysfunction was lower in patients treated with **SPRYCEL<sup>®</sup>** 100mg once daily than in those treated with **SPRYCEL<sup>®</sup>** 70mg twice daily (Table 3a). Myelosuppression was also reported less frequently with the 100mg once daily (see **Laboratory abnormalities**, Table 6).

**Table 3a: Selected Adverse Drug Reactions Reported in Phase III Dose-Optimisation Study: Chronic Phase CML**

	100mg once daily n = 165		140mg once daily <sup>a</sup> n = 163		50mg twice daily <sup>a</sup> n = 167		70mg twice daily <sup>a</sup> n = 167	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
<b>Preferred Term</b>	<b>Percent (%) of Patients</b>							
<b>Diarrhoea</b>	27	2	30	4	31	2	27	4
<b>Fluid Retention</b>	34	4	40	7	37	5	40	10
Superficial Oedema	18	0	17	1	19	0	19	1
Pleural Effusion	18	2	26	5	24	4	24	5
Generalised Oedema	3	0	5	0	0	0	2	0
Congestive heart failure/cardiac dysfunction <sup>b</sup>	0	0	4	1	1	1	5	3
Pericardial effusion	2	1	6	2	5	2	2	1
Pulmonary Oedema	0	0	0	0	1	1	3	1
Pulmonary hypertension	0	0	1	0	1	0	1	1
<b>Haemorrhage</b>	11	1	14	1	10	4	16	2
Gastrointestinal bleeding	2	1	2	0	5	3	4	2

<sup>a</sup> Not a recommended starting dosage of **SPRYCEL**<sup>®</sup> for chronic phase CML

<sup>b</sup> Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL (median duration of treatment of 14 months (range <1-36 months) for accelerated phase CML; 3 months (range <1-32 months) for myeloid blast CML; 4 months (<1-22 months) for lymphoid blast CML; and 3 months (<1-29 months) for Ph +ALL), fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with **SPRYCEL**<sup>®</sup> 140mg once daily than in those treated with 70mg twice daily (Table 3b).

**Table 3b: Selected Adverse Drug Reactions Reported in Phase III Dose-Optimisation Study: Advanced Phase CML and Ph+ ALL**

Preferred Term	140mg once daily n = 304		70mg twice daily <sup>a</sup> n = 305	
	All Grades	Grade 3/4	All Grades	Grade 3/4
	<b>Percent (%) of Patients</b>			
<b>Diarrhoea</b>	28	3	29	4
<b>Fluid Retention</b>	33	7	43	11
Superficial oedema	15	<1	19	1
Pleural Effusion	20	6	34	7
Generalised oedema	2	0	3	1
Congestive heart failure/cardiac dysfunction <sup>b</sup>	1	0	2	1
Pericardial effusion	2	1	6	2
Pulmonary oedema	1	1	3	1
Ascites	0	0	1	0
Pulmonary hypertension	0	0	1	<1
<b>Haemorrhage</b>	23	8	27	7
Gastrointestinal bleeding	8	6	12	6

<sup>a</sup> Not a recommended starting dosage of **SPRYCEL**<sup>®</sup> for advanced phase CML

<sup>b</sup> Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

The following adverse reactions were reported in patients in **SPRYCEL**<sup>®</sup> clinical trials. These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* ( $\geq 1/10$ ); *common* ( $\geq 1/100$  to  $< 1/10$ ); *uncommon* ( $\geq 1/1,000$  to  $< 1/100$ ); *rare* ( $\geq 1/10,000$  to  $< 1/1,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

### Investigations

*Common:* weight decreased, weight increased

### Cardiac disorders

*Common:* congestive heart failure/cardiac dysfunction<sup>a</sup>, pericardial effusion, arrhythmia (including tachycardia), palpitations

*Uncommon:* electrocardiogram QT prolonged, myocardial infarction (including fatal outcomes), pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly

*Rare:* cor pulmonale, myocarditis, acute coronary syndrome

### Blood and lymphatic system disorders

*Common:* febrile neutropenia, pancytopenia

*Rare:* aplasia pure red cell

**Nervous system disorders**

*Very Common:* headache

*Common:* neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence

*Uncommon:* CNS bleeding<sup>b</sup>, syncope, tremor, amnesia

*Rare:* cerebrovascular accident, transient ischemic attack, convulsion, optic neuritis

**Eye disorders**

*Common:* visual disorder, (including visual disturbance, vision blurred, and visual acuity reduced) dry eye

*Uncommon:* conjunctivitis

**Ear and labyrinth disorders**

*Common:* tinnitus

*Uncommon:* vertigo

**Respiratory, thoracic and mediastinal disorders**

*Very Common:* pleural effusion, dyspnea

*Common:* cough, pulmonary oedema, lung infiltration, pneumonitis, pulmonary hypertension

*Uncommon:* bronchospasm, asthma

*Rare:* acute respiratory distress syndrome,

**Gastrointestinal disorders**

*Very Common:* diarrhoea, nausea, vomiting, abdominal pain

*Common:* colitis (including neutropenic colitis), gastritis, dyspepsia, constipation, abdominal distension, oral soft tissue disorder, gastrointestinal bleeding, mucosal inflammation (including mucositis/stomatitis)

*Uncommon:* pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia

*Rare:* protein-losing gastroenteropathy

**Renal and urinary disorders**

*Uncommon:* renal failure, urinary frequency, proteinuria

**Skin and subcutaneous tissue disorders**

*Very Common:* skin rash<sup>c</sup>

*Common:* pruritis, alopecia, dermatitis (including eczema), acne, dry skin, urticaria, hyperhidrosis

*Uncommon:* acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome

**Musculoskeletal and connective tissue disorders**

*Very Common:* musculoskeletal pain

*Common:* muscle inflammation, muscular weakness, arthralgia, myalgia,

*Uncommon:* musculoskeletal stiffness, rhabdomyolysis, blood creatine phosphokinase increased

*Rare:* tendonitis

**Metabolism and nutrition disorders**

*Common:* appetite disturbances, anorexia

*Uncommon:* hyperuricaemia, hypoalbuminaemia

### **Infections and infestations**

*Very Common:* infection (including bacterial, viral, fungal, non-specified)

*Common:* pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection

*Uncommon:* sepsis (including fatal outcome)

### **Injury, poisoning, and procedural complications**

*Common:* contusion

### **Neoplasms benign, malignant and unspecified (including cysts and polyps)**

*Uncommon:* tumour lysis syndrome

### **Vascular disorders**

*Very Common:* haemorrhage<sup>d</sup>

*Common:* hypertension, flushing

*Uncommon:* hypotension, thrombophlebitis

*Rare:* livedo reticularis

### **General disorders and administration site conditions**

*Very Common:* fluid retention, fatigue, superficial oedema<sup>e</sup>, pyrexia

*Common:* asthenia, pain, generalised oedema, chest pain, chills

*Uncommon:* malaise, temperature intolerance

### **Immune System Disorders**

*Uncommon:* hypersensitivity (including erythema nodosum)

### **Hepatobiliary disorders**

*Uncommon:* hepatitis, cholecystitis, cholestasis

### **Reproductive system and breast disorders**

*Uncommon:* gynecomastia, irregular menstruation

### **Psychiatric disorders**

*Common:* depression, insomnia

*Uncommon:* anxiety, confusional state, affect lability, libido decreased

a. Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy,

diastolic dysfunction, ejection fraction decreased and ventricular failure.

b. Includes cerebral hematoma, cerebral haemorrhage, extradural hematoma, haemorrhage intracranial, hemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

c. Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, fungal rash, generalised erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash, papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation and urticaria vesiculosa.

d. Excludes gastrointestinal bleeding and CNS bleeding; these ADRs are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

e. Includes auricular swelling, conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, genital swelling, gravitational oedema, lip oedema, localised oedema, macular oedema, oedema genital, oedema mouth, oedema peripheral, orbital

oedema, penile oedema, periorbital oedema, pitting oedema, scrotal oedema, swelling face and tongue oedema.

## Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of **SPRYCEL**<sup>®</sup>. 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.

Cardiac disorders:	atrial fibrillation/atrial flutter <sup>a</sup>
Vascular disorders:	thrombosis/embolism (including pulmonary embolism, deep vein thrombosis) <sup>b</sup>
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease, pulmonary arterial hypertension
Gastrointestinal disorders:	fatal gastrointestinal hemorrhage <sup>c</sup>

a. Typically reported in elderly patients or in patients with confounding factors including significant underlying or concurrent cardiac or cardiovascular disorders, or other significant comorbidities (eg, severe infection/sepsis, electrolyte abnormalities).

b. Typically reported in patients with underlying malignancies or other confounding risk factors, including cardiovascular disorders, history of surgery, or other comorbidities.

c. Typically reported in patients with progressive underlying malignancies (eg, advanced phase CML or Ph+ ALL) or severe or life-threatening comorbidities (eg, severe gastrointestinal disorders, infection or sepsis, thrombocytopenia).

## Laboratory Abnormalities

### *Haematology and Biochemistry in patients with newly diagnosed chronic phase CML*

The comparative frequency of Grade 3 and 4 laboratory abnormalities in patients with newly diagnosed chronic phase CML is presented in Table 4. There were no discontinuations of **SPRYCEL**<sup>®</sup> therapy due to these biochemical laboratory parameters.

**Table 4: CTC Grade 3/4 Laboratory Abnormalities in Patients with Newly Diagnosed Chronic Phase CML**

	<b>SPRYCEL®</b> n= 258	<b>imatinib</b> n= 258
<b>Percent (%) of Patients</b>		
<b>Haematology Parameters</b>		
Neutropenia	21	20
Thrombocytopenia	19	11
Anaemia	10	7
<b>Biochemistry Parameters</b>		
Hypophosphataemia	4	21
Hypokalaemia	0	2
Hypocalcaemia	< 1	< 1
Elevated SGPT (ALT)	< 1	1
Elevated SGOT (AST)	< 1	1
Elevated Bilirubin	1	0
Elevated Creatinine	< 1	1

CTC grades: neutropenia (Grade 3  $\geq 0.5 - < 1.0 \times 10^9/l$ , Grade 4  $< 0.5 \times 10^9/l$ ); thrombocytopenia (Grade 3  $\geq 25 - < 50 \times 10^9/l$ , Grade 4  $< 25 \times 10^9/l$ ); anaemia (haemoglobin Grade 3  $\geq 65 - < 80$  g/l, Grade 4  $< 65$  g/l); elevated creatinine (Grade 3  $> 3 - 6 \times$  upper limit of normal range (ULN), Grade 4  $> 6 \times$  ULN); elevated bilirubin (Grade 3  $> 3 - 10 \times$  ULN, Grade 4  $> 10 \times$  ULN); elevated SGOT or SGPT (Grade 3  $> 5 - 20 \times$  ULN, Grade 4  $> 20 \times$  ULN); hypocalcaemia (Grade 3  $< 7.0 - 6.0$  mg/dl, Grade 4  $< 6.0$  mg/dl); hypophosphataemia (Grade 3  $< 2.0 - 1.0$  mg/dl, Grade 4  $< 1.0$  mg/dl); hypokalaemia (Grade 3  $< 3.0 - 2.5$  mmol/l, Grade 4  $< 2.5$  mmol/l).

*Haematology and Biochemistry in patients with resistance or intolerance to prior imatinib therapy:*

Table 5 shows laboratory findings from **SPRYCEL®** clinical trials in which 2,182 patients with CML and imatinib resistance or intolerance received **SPRYCEL®** for a median of 15 months.

**Table 5: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies in Patients with Resistance or Intolerance to Prior Imatinib Therapy**

	Chronic Phase (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase (n=115)	Ph+ ALL (n=135)
Percent (%) of Patients					
<b>Hematology Parameters</b>					
Neutropenia	47	69	80	83	75
Thrombocytopenia	41	72	82	86	71
Anemia	19	55	75	51	42
<b>Biochemistry Parameters</b>					
Hypophosphatemia	10	14	20	19	21
Hypokalemia	3	10	20	13	16
Hypocalcemia	2	8	16	14	9
Elevated SGPT (ALT)	1	4	6	7	7
Elevated SGOT (AST)	1	1	4	5	4
Elevated Bilirubin	1	1	4	7	2
Elevated Creatinine	1	1	4	2	0

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

Myelosuppression was commonly reported in all patient populations. In newly diagnosed chronic phase CML, myelosuppression was less frequently reported than in chronic phase CML patients with resistance or intolerance to prior imatinib therapy. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anaemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML.

In patients who experienced Grade 3 or 4 myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 1.6% of newly diagnosed chronic phase CML patients and in 5% of patients with resistance or intolerance to prior imatinib therapy.

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in the Phase III dose-optimisation study patients with chronic phase CML are shown in Table 6.

**Table 6: CTC Grades 3/4 Laboratory Abnormalities in Phase III Dose –Optimization Study \*(Chronic Phase CML)**

	100mg QD (n=165)	140mg QD <sup>a</sup> (n=163)	50mg BID <sup>a</sup> (n=167)	70mg BID <sup>a</sup> (n=167)
Percent (%) of Patients				
<b>Hematology Parameters</b>				
Neutropenia	36	44	47	46
Thrombocytopenia	23	41	36	38
Anemia	13	19	18	19
<b>Biochemistry Parameters</b>				
Hypophosphataemia	10	6	9	9
Hypokalaemia	2	4	2	4
Hypocalcaemia	1	3	0	3
Elevated SGPT (ALT)	0	1	1	1
Elevated SGOT (AST)	1	1	1	0
Elevated Bilirubin	1	1	0	1
Elevated Creatinine	0	1	0	1

<sup>a</sup> Not a recommended starting dosage of SPRYCEL<sup>®</sup> for chronic phase CML

CTC grades: neutropenia (Grade 3  $\geq 0.5$ – $1.0 \times 10^9/L$ , Grade 4  $< 0.5 \times 10^9/L$ ); thrombocytopenia (Grade 3  $\geq 25$ – $< 50 \times 10^9/L$ , Grade 4  $< 25 \times 10^9/L$ ); anaemia (haemoglobin Grade 3  $\geq 65$ – $< 80$  g/L, Grade 4  $< 65$  g/L); elevated creatinine (Grade 3  $> 3$ – $6 \times$  upper limit of normal range (ULN), Grade 4  $> 6 \times$  ULN); elevated bilirubin (Grade 3  $> 3$ – $10 \times$  ULN, Grade 4  $> 10 \times$  ULN); elevated SGOT or SGPT (Grade 3  $> 5$ – $20 \times$  ULN, Grade 4  $> 20 \times$  ULN); hypocalcaemia (Grade 3  $< 7.0$ – $6.0$  mg/dL, Grade 4  $< 6.0$  mg/dL); hypophosphataemia (Grade 3  $< 2.0$ – $1.0$  mg/dL, Grade 4  $< 1.0$  mg/dL); hypokalaemia (Grade 3  $< 3.0$ – $2.5$  mmol/L, Grade 4  $< 2.5$  mmol/L).

## Medicine Classification

Prescription Medicine.

## Package Quantities

20mg, 50mg, and 70mg tablets are available in bottles or blisters of 60 tablets. 100mg tablets are available in bottles or blisters of 30 tablets.

## Further Information

**Dasatinib** is a white to off-white powder. The drug substance is insoluble in water (0.008mg/mL) at  $24 \pm 4^\circ\text{C}$ . The pH of a saturated solution of **dasatinib** in water is about 6.0. Two basic ionization constants ( $\text{pK}_a$ ) were determined to be 6.8 and 3.1, and one weakly acidic  $\text{pK}_a$  was determined to be 10.8. The solubilities of **dasatinib** in various solvents at  $24 \pm 4^\circ\text{C}$  are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil.

## Storage

SPRYCEL<sup>®</sup> should be stored below  $30^\circ\text{C}$ .

## **Name And Address**

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## **Date Of Preparation**

26 July 2011

(Sprycel 10.0)