Bristol Myers Squibb

SPRYCEL®

(dasatinib) Tablets

1 INDICATIONS AND USAGE

SPRYCEL® (dasatinib) is indicated for the treatment of adult patients with

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

SPRYCEL® (dasatinib) is indicated for the treatment of pediatric patients with

- newly diagnosed Ph+ CML in chronic phase or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

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

2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL

The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.

Do not crush, cut or chew tablets. Swallow tablets whole. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole. Dispersal of tablets shows a reduction in exposure of dasatinib based on limited clinical data *[see Use in Specific Populations (8.3) and Clinical Pharmacology (11)]*.

There is no experience with SPRYCEL treatment in children under 1 year of age.

Table 1: Dosage of SPRYCEL Tablets for Pediatric Patients[a]

Body Weight (kg)[b]	Daily Dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

[a] For pediatric patients with Ph+ ALL, begin SPRYCEL therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.

[b] Tablet dosing is not recommended for patients weighing less than 10 kg.

Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph+ ALL, and pediatric patients with CML.

2.3 Dose Modification

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity *[see Drug Interactions (7.2)]*.

Strong CYP3A4 inhibitors: Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily.
- 20 mg daily for patients taking SPRYCEL 100 mg daily.
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased. *[See Drug Interactions (7.1).]*

2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML

For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below). Dose escalation is not recommended for pediatric patients with Ph+ ALL, where SPRYCEL is administered in combination with chemotherapy.

Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients with chronic phase CML who do not achieve a hematologic or cytogenetic response at the recommended starting dosage at the recommended time points, per current treatment guidelines, and who tolerate the treatment.

Table 2: Dose Escalation for Paediatric Patients with CML

Formulation	**Dose (maximum dose per day)**	
	Starting Dose	**Escalation**
Tablets	40 mg	50 mg
	60mg	70 mg
	70 mg	90 mg
	100 mg	120 mg

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 adults and pediatric patients are summarized in Tables 3 and 4, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

Chronic Phase CML (starting dose 100 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<50 \times 10^9$/L	1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. 3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.

*ANC: absolute neutrophil count

Table 4: Dose Adjustment for Neutropenia and Thrombocytopenia in Pediatric Patients with Ph+ CML

	Tablet Dose (maximum dose per day)		
	Original Starting Dose	**One-Level Dose Reduction**	**Two-Level Dose Reduction**
1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC* $\geq 1.0 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L and resume at the original starting dose or at a reduced dose. 3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose.	40 mg	20 mg	**
	60 mg	40 mg	20 mg
	70 mg	60 mg	50 mg
	100 mg	80 mg	70 mg

*ANC: absolute neutrophil count
** lower tablet dose not available

For pediatric patients with chronic phase CML, 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.

For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and resume at the same dose level once the next block of treatment is started. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another 7 days, perform a bone marrow assessment to assess cellularity and percentage of blasts. If marrow cellularity is <10%, interrupt treatment with SPRYCEL until ANC >500/μL (0.5×10^9/L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with SPRYCEL may be considered.

Non-hematological adverse reactions

If a moderate (Grade 2) non-hematologic adverse reaction develops with SPRYCEL, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe (Grade 3 or 4) 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)]*.

For adult patients with chronic phase CML who received 100 mg once daily, dose reduction to 80 mg once daily with further reduction from 80 mg once daily to 50 mg once daily, if needed, is recommended. For adult patients with advanced phase CML or Ph+ ALL who received 140 mg once daily, dose reduction to 100 mg once daily with further reduction from 100 mg once daily to 50 mg once daily, if needed, is recommended.

For pediatric patients with chronic phase CML who develop non-hematologic adverse reactions, the dose reduction recommendations for hematologic adverse reactions that are described above should be followed.

For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade ≥ 3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade ≤1. For elevated direct bilirubin over 5 times the institutional upper limit of normal (ULN), interrupt treatment until improvement to baseline or grade ≤1. For elevated AST/ALT over 15 times the institutional ULN, interrupt treatment until improvement to baseline or grade <1. For recurrent liver function test abnormalities as above, reduce the dose if this adverse reaction recurs after reinitiation of SPRYCEL. Dose reduction recommendations are described in Table 5.

Table 5: Dose Adjustments for Non-Hematologic Toxicities in Pediatric Patients

	Tablet Dose (maximum dose per day)		
	Original Starting Dose	**One-Level Dose Reduction**	**Two-Level Dose Reduction**
1. If a non-hematologic toxicity grade 2 occurs, consider interrupting SPRYCEL if no recovery despite symptomatic therapy; once recovered to grade ≤1, resume at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events.	40 mg	20 mg	**
	60 mg	40 mg	20 mg
2. If a non-hematologic toxicity grade 3 occurs, stop SPRYCEL until recovery to grade ≤1 and then resume at a reduced dose.	70 mg	60 mg	50 mg
	100 mg	80 mg	70 mg
3. If direct bilirubin is >5 ULN or AST/ALT >15 ULN, interrupt SPRYCEL until recovery to grade ≤1 and then resume SPRYCEL at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events.			

** lower tablet dose not available

2.6 Duration of Treatment

In clinical studies, treatment with SPRYCEL in adults and in pediatric patients with chronic phase CML 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 MR4.5) has not been established.

In clinical studies, treatment with SPRYCEL in pediatric patients with Ph+ ALL was administered for a maximum duration of 2 years *[see Dosage and Administration (2.2) and Clinical Studies (13)]*.

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, or 70-mg white to off-white, biconvex, film-coated tablets. *[See How Supplied (15.1).]*

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with thrombocytopenia, neutropenia, and anemia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In patients with advanced phase CML or Ph+ ALL, complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. In patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated.

In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily or dose reduction *[see Dosage and Administration (2.3)* and *Adverse Reactions (6)]*.

5.2 Bleeding

In patients with chronic phase CML (n=548), 5 patients (1%) receiving SPRYCEL had grade 3 or 4 hemorrhage. In patients with advanced phase CML or Ph+ ALL, severe (Grade 3 or 4) central nervous system (CNS) hemorrhages occurred in 1% of patients receiving SPRYCEL at the recommended dose (n=304). One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal hemorrhage occurred in 6% of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 hemorrhage occurred in 2% of patients with advanced phase CML. Most bleeding events in these patients were associated with severe thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that SPRYCEL treatment reversibly affects platelet activation.

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

5.3 Fluid Retention

SPRYCEL is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML study, grade 3 or 4 fluid retention was reported in 13 patients (5%) in the dasatinib group and in 2 patients (1%) in the imatinib-treatment group after a minimum of 60 months follow-up *[see Adverse Reactions (6)]*. In all SPRYCEL-treated patients with chronic phase CML, severe fluid retention occurred in 32 patients (6%) receiving SPRYCEL at the recommended dose. In clinical trials in patients with advanced phase CML, grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 1% of patients, respectively. In these patients, grade 3 or 4 pulmonary edema and pulmonary hypertension were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. Patients aged 65 years and older are more likely than younger patients to experience pleural effusion, dyspnoea, cough, pericardial effusion and congestive heart failure, and should be monitored closely.

5.4 QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In 258 patients treated with SPRYCEL and 258 patients treated with imatinib with a minimum of 60 months follow-up in the Phase III study of 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-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (<1%) in each group experienced a QTcF >500 msec. In 865 patients with leukemia treated with SPRYCEL in Phase 2 clinical studies, 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 2182 patients with resistance or intolerance to prior imatinib therapy who received SPRYCEL in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one of these patients (1%) experienced a QTcF >500 msec.

SPRYCEL should be administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to SPRYCEL administration.

5.5 Cardiac Adverse Reactions

SPRYCEL was studied in a randomized 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, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking SPRYCEL. Adverse cardiac events were more frequent in patients with risk factors or a 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.

5.6 Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterization, has been reported in association with SPRYCEL treatment. In these cases, PAH was reported after initiation of SPRYCEL therapy, including after more than one year of treatment. Patients with PAH reported during SPRYCEL 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 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 (2.3)]*. 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 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-treated patients with PAH following cessation of SPRYCEL therapy.

5.7 Embryofetal Toxicity

SPRYCEL can cause fetal harm when administered to a pregnant woman. There have been reports of spontaneous abortion and fetal and infant anomalies from women who have taken SPRYCEL during pregnancy. In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities, including skeletal malformations, were observed in rats and rabbits. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SPRYCEL.

Sexually active male or female patients of child bearing potential taking SPRYCEL should use adequate contraception.

If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus. *[see Use in Specific Populations (8.1)]*.

5.8 Severe Dermatologic Reactions

Individual cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in patients treated with SPRYCEL. Stevens-Johnson syndrome has been reported in post-marketing cases for which it could not be determined whether the reactions were directly related to SPRYCEL or to concomitant medications. SPRYCEL should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

5.9 Hepatitis B Virus Reactivation

BCR-ABL TKIs have been associated with hepatitis B virus (HBV) reactivation including individual case reports for SPRYCEL. In some instances, HBV reactivation occurring in conjunction with other BCR-ABL TKIs resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Screening for HBV should be considered in accordance with published guidelines before starting therapy with SPRYCEL. Consultation with a physician with expertise in the treatment of HBV is recommended for patients who test positive for HBV serology.

Patients who are carriers of HBV and require treatment with BCR-ABL TKIs should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop reactivation of HBV while receiving SPRYCEL prompt consultation with a physician with expertise in the treatment of HBV is recommended.

5.10 Effects on Growth and Development in Pediatric Patients

In pediatric trials of SPRYCEL in imatinib-resistant/intolerant chronic phase Ph+ CML pediatric patients and treatment-naive chronic phase Ph+ CML pediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopenia,

growth retardation, and gynecomastia (see section 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

In pediatric trials of SPRYCEL in combination with chemotherapy in newly diagnosed Ph+ ALL pediatric patients after a maximum of 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 1 (0.6%) patient. This case was a Grade 1 osteopenia.

6 ADVERSE REACTIONS

SPRYCEL as single-agent therapy

The data described below reflect the exposure to SPRYCEL as single-agent therapy at all doses tested in clinical studies (N=2,900), including 324 adult patients with newly diagnosed chronic phase CML, 2,388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 188 pediatric patients. In the 2,712 adult patients with either chronic phase CML, advanced phase CML or Ph+ ALL, the median duration of therapy 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 1,618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months). The median duration of therapy in 1,094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months). Among 188 patients in paediatric studies, the median duration of therapy was 26.3 months (range 0 to 99.6 months). In the subset of 130 chronic phase CML SPRYCEL-treated pediatric patients, which included patients receiving SPRYCEL tablets and patients receiving a powder for oral suspension formulation of SPRYCEL, the median duration of therapy was 42.3 months (range 0.1 to 99.6 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. In the overall population of 2,712 SPRYCEL-treated adult patients, 520 (19%) experienced adverse reactions leading to treatment discontinuation.

The overall safety profile of SPRYCEL in the pediatric chronic phase Ph+ CML population was similar to that of the adult population, regardless of formulation, with the exception of no reported pericardial effusion, pleural effusion, pulmonary edema, or pulmonary hypertension in the pediatric population. Of the 130 SPRYCEL-treated pediatric subjects with chronic phase CML, 2 (1.5%) experienced adverse reactions leading to treatment discontinuation.

Tabulated Summary of Adverse Reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients treated with SPRYCEL used as single-agent therapy in clinical studies and postmarketing experience (Table 6). These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* (≥1/10); *common* (≥1/100 to <1/10); *uncommon* (≥1/1,000 to <1/100); *rare* (≥1/10,000 to <1/1,000); *not known* (cannot be estimated from

available postmarketing data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6: Tabulated Summary of Adverse Reactions

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 (including cytomegalovirus – CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Not known	hepatitis B reactivation
Blood and lymphatic system disorders	
Very common	myelosuppresion (including anemia, neutropenia, thrombocytopenia)
Common	febrile neutropenia
Uncommon	lymphadenopathy, lymphopenia
Rare	aplasia pure red cell
Immune System Disorders	
Uncommon	hypersensitivity (including erythema nodosum)
Rare	anaphylactic shock[a]
Endocrine Disorders	
Uncommon	hypothyroidism
Rare	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
Common	appetite disturbances[b], hyperuricaemia
Uncommon	tumor lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
Rare	diabetes mellitus
Psychiatric disorders	
Common	depression, insomnia
Uncommon	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
Very common	headache
Common	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Uncommon	CNS bleeding*[c], syncope, tremor, amnesia, balance disorder
Rare	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
Common	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Uncommon	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
Common	tinnitus
Uncommon	hearing loss, vertigo
Cardiac disorders	
Common	congestive heart failure/cardiac dysfunction*[d], pericardial effusion*, arrhythmia (including tachycardia), palpitations

Uncommon	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
Rare	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Not known	atrial fibrillation/atrial flutter
Vascular disorders	
Very common	haemorrhage*[e]
Common	hypertension, flushing
Uncommon	hypotension, thrombophlebitis, thrombosis
Rare	deep vein thrombosis, embolism, livedo reticularis
Not known	thrombotic microangiopathy (TMA)
Respiratory, thoracic, and mediastinal disorders	
Very common	pleural effusion*, dyspnoea
Common	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
Uncommon	pulmonary arterial hypertension, bronchospasm, asthma
Rare	pulmonary embolism, acute respiratory distress syndrome
Not known	interstitial lung disease
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain
Common	gastrointestinal bleeding*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Uncommon	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
Rare	protein-losing gastroenteropathy, ileus, anal fistula
Not known	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
Uncommon	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	skin rash[f]
Common	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
Rare	leukocytoclastic vasculitis, skin fibrosis
Not known	Stevens-Johnson syndrome[g]
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain
Common	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Uncommon	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
Rare	epiphyses delayed fusion[h], growth retardation[h]
Pregnancy, puerperium and perinatal conditions	
Rare	abortion

Renal and urinary disorders	
Uncommon	renal impairment (including renal failure), urinary frequency, proteinuria
Not known	nephrotic syndrome
Reproductive system and breast disorders	
Uncommon	gynecomastia, menstrual disorder
General disorders and administration site conditions	
Very common	peripheral edema[i], fatigue, pyrexia, face edema[j]
Common	asthenia, pain, chest pain, generalized edema*[k], chills
Uncommon	malaise, other superficial edema[l]
Rare	gait disturbance
Investigations	
Common	weight decreased, weight increased
Uncommon	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
Common	contusion

[a] Reported only in pediatric studies.

[b] Includes decreased appetite, early satiety, increased appetite.

[c] Includes central nervous system hemorrhage, cerebral hematoma, cerebral hemorrhage, extradural hematoma, hemorrhage intracranial, hemorrhagic stroke, subarachnoid hemorrhage, subdural hematoma, and subdural hemorrhage.

[d] Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesis.

[e] Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders organ class, respectively.

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

[g] In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to SPRYCEL or to concomitant medicinal product.

[h] Reported only in pediatric studies. Frequency reported as common in pediatric studies vs rare in overall monotherapy population.

[i] gravitational edema, localized edema, edema peripheral

[j] conjunctival edema, eye edema, eye swelling, eyelid edema, face edema, lip oedema, macular edema, edema mouth, orbital edema, periorbitali edema, swelling face

[k] fluid overload, fluid retention, gastrointestinal edema, generalized edema, peripheral swelling (reported only in pediatric studies), edema, edema due to cardiac disease, perinephric effusion, post procedural edema, visceral edema.

[l] genital swelling, incision site edema, edema genital, penile edema, penile swelling, scrotal edema, skin swelling, testicular swelling, vulvovaginal swelling.

* For additional details, see section "Description of selected adverse reactions"

Description of selected adverse reactions

Myelosuppression

Treatment with SPRYCEL is associated with anemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML *[see Warnings and Precautions (5.1)]*.

Bleeding

Bleeding drug-related events, ranging from petechiae and epistaxis to grade 3 or 4 gastrointestinal hemorrhage and CNS bleeding, were reported in patients taking SPRYCEL *[see Warnings and Precautions (5.2)]*.

Fluid retention

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary edema and pericardial effusion with or without superficial edema may be collectively described as "fluid retention". In the newly diagnosed chronic phase CML study after a minimum of 60 months follow-up, SPRYCEL-related fluid retention events included pleural effusion (28%), superficial edema (14%), pulmonary hypertension (5%), generalized edema (4%) and pericardial effusion (4%). Congestive heart failure/cardiac dysfunction and pulmonary edema were reported in <2% of patients.

The cumulative rate of SPRYCEL-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, 24% at 48 months and 28% at 60 months. A total of 46 SPRYCEL-treated patients had recurrent pleural effusions. Seventeen patients had 2 separate events, 6 had 3 events, 18 had 4 to 8 events and 5 had > 8 episodes of pleural effusions. The median time to first SPRYCEL-related grade 1 or 2 pleural effusion was 114 weeks (range: 4 to 299 weeks). Less than 10% of patients with pleural effusion had severe (grade 3 or 4) SPRYCEL-related pleural effusions. The median time to first occurrence of grade ≥ 3 dasatinib-related pleural effusion was 175 weeks (range: 114 to 274 weeks). The median duration of SPRYCEL-related pleural effusion (all grades) was 283 days (~40 weeks).
Pleural effusion was usually reversible and managed by interrupting SPRYCEL treatment and using diuretics or other appropriate supportive care measures (see sections 4.2 and 4.4). Among dasatinib-treated patients with drug-related pleural effusion (n=73), 45 (62%) had dose interruptions and 30 (41%) had dose reductions. Additionally, 34 (47%) received diuretics, 23 (32%) received corticosteroids, and 20 (27%) received both corticosteroids and diuretics. Nine (12%) patients underwent therapeutic thoracentesis.
Six percent of SPRYCEL-treated patients discontinued treatment due to drug-related pleural effusion. Pleural effusion did not impair the ability of patients to obtain a response. Among the SPRYCEL-treated patients with pleural effusion, 96% achieved a cCCyR, 82% achieved a MMR, and 50% achieved a MR4.5 despite dose interruptions or dose adjustment.
For further information on patients with chronic phase CML and advanced phase CML or Ph+ ALL, see *Warnings and Precautions (5.3).*

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterization, has been reported in association with dasatinib exposure. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medications or had comorbidities in

addition to the underlying malignancy. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following discontinuation of dasatinib.

QT Prolongation

In the Phase III study in patients with newly diagnosed chronic phase CML, one patient (<1%) of the SPRYCEL-treated patients had a QTcF >500 msec after a minimum of 12 months follow-up *[see Warnings and Precautions (5.4)]*. No additional patients were reported to have QTcF >500 msec after a minimum of 60 months follow-up.

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 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 in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF >500 msec *[see Warnings and Precautions (5.4)]*.

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases occurring in conjunction with other BCR-ABL TKIs resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome [*see Warnings and Precautions (5.9)*].

Cardiac adverse reactions

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 (5.5)]*.

SPRYCEL in combination with chemotherapy
Pediatric patients with Ph+ ALL

In addition, there were two studies in a total of 161 pediatric patients with Ph+ ALL in which SPRYCEL was administered in combination with chemotherapy. In the pivotal study, 106 pediatric patients received SPRYCEL in combination with chemotherapy on a continuous dosing regimen. In a supportive study, of 55 pediatric patients, 35 received SPRYCEL in combination with chemotherapy on a discontinuous dosing regimen (two weeks on treatment followed by one to two weeks off) and 20 received SPRYCEL in combination with chemotherapy on a continuous dosing regimen. Among the 126 Ph+ ALL pediatric patients treated with SPRYCEL on a continuous dosing regimen, the median duration of therapy was 23.6 months (range 1.4 to 33 months).

Of the 126 Ph+ ALL pediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in these two pediatric studies at a frequency of ≥10% in patients on a continuous dosing regimen are shown

in Table 7. Of note, pleural effusion was reported in 7 (5.6%) patients in this group, and is therefore not included in the table.

Table 7: Adverse reactions reported in ≥10% of pediatric patients with Ph+ ALL treated with SPRYCEL on a continuous dosing regimen in combination with chemotherapy (N=126)[a]

	Percent (%) of patients	
Adverse reaction	**All grades**	**Grade 3/4**
Febrile neutropenia	27.0	26.2
Nausea	20.6	5.6
Vomiting	20.6	4.8
Abdominal pain	14.3	3.2
Diarrhea	12.7	4.8
Pyrexia	12.7	5.6
Headache	11.1	4.8
Decreased appetite	10.3	4.8
Fatigue	10.3	0

[a] In the pivotal study, among 106 total patients, 24 patients received the powder for oral suspension at least once, 8 of whom received the powder for oral suspension formulation exclusively.

Laboratory test abnormalities

Hematology 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 8. There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.

Table 8: CTC Grade 3/4 Laboratory Abnormalities in a Phase III Study of Patients with Newly Diagnosed Chronic Phase CML

	SPRYCEL n= 258	**Imatinib n= 258**
	Percent (%) of patients	
Hematology parameters		
Neutropenia	29	24
Thrombocytopenia	22	14
Anemia	13	9
Biochemistry parameters		
Hypophosphatemia	7	31
Hypokalemia	0	3
Hypocalcemia	4	3
Elevated SGPT (ALT)	<1	2
Elevated SGOT (AST)	<1	1
Elevated bilirubin	1	0
Elevated creatinine	1	1

CTC grades: neutropenia (Grade 3 ≥0.5 – <1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25 – <50 × 10^9/L, Grade 4 <25 × 10^9/L); anemia (hemoglobin Grade 3 ≥65 – <80 g/L, Grade 4 <65 g/L); elevated

creatinine (Grade 3 >3 – 6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3 – 10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5 – 20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0 – 6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0 – 1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0 – 2.5 mmol/L, Grade 4 <2.5 mmol/L).

In SPRYCEL-treated patients with newly diagnosed chronic phase CML who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 1.6% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of permanent discontinuation due to grade 3 or 4 myelosuppression was 2.3%.

Hematology and Biochemistry in patients with resistance or intolerance to prior imatinib therapy

Hematology:

In CML, cytopenias (thrombocytopenia, neutropenia, and anemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of Grade 3 or 4 hematologic abnormalities is presented in Table 9.

Table 9: CTC Grades 3/4 Hematological Laboratory Abnormalities in Clinical Studies in patients with resistance or intolerance to prior imatinib therapy

	Chronic Phase (n=165)[b]	Accelerated Phase (n=157)[c]	Myeloid Blast Phase (n=74)[c]	Lymphoid Blast Phase and Ph+ ALL (n=168)[c]
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	36	58	77	76
Thrombocytopenia	23	63	78	74
Anemia	13	47	74	44

[a] Phase 3 dose optimization study results reported at 2 year study follow up.

[b] CA180-034 study results in recommended starting dose of 100 mg once daily.

[c] CA180-035 study results in recommended starting dose of 140 mg once daily

CTC grades: neutropenia (Grade 3 ≥0.5 – <1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25 – <50 × 10^9/L, Grade 4 <25 × 10^9/L); anemia (hemoglobin Grade 3 ≥65 – <80 g/L, Grade 4 <65 g/L).

Cumulative grade 3 or 4 cytopenias among patients treated with 100 mg once daily were similar at 2 and 5 years including: neutropenia (35% vs. 36%), thrombocytopenia (23% vs. 24%) and anaemia (13% vs. 13%).

In patients who experienced Grade 3 or 4 myelosuppression, recovery generally occurred following dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 5% of patients. Most patients continued treatment without further evidence of myelosuppression.

Biochemistry (2 year follow-up) In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphatemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in ≤1% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of grade 3

or 4 hypophosphatemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained 1%. There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.

2 year follow-up:

Grade 3 or 4 elevations of transaminase or bilirubin were reported in 1% of patients with chronic phase CML but elevations were reported with an increased frequency of 1% to 7% of patients with advanced phase CML and Ph+ ALL. It was usually managed with dose reduction or interruption. In the Phase 3 dose-optimisation study in chronic phase CML, Grade 3 or 4 elevations of transaminases or bilirubin were reported in ≤1% of patients with similar low incidence in the four treatment groups. In the Phase 3 dose-optimisation study in advanced phase CML and Ph+ ALL, Grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% to 5% of patients across treatment groups.

Approximately 5% of the SPRYCEL-treated patients who had normal baseline levels experienced grade 3 or 4 transient hypocalcemia at some time during the course of the study. In general, there was no association of decreased calcium with clinical symptoms. Patients developing grade 3 or 4 hypocalcemia often had recovery with oral calcium supplementation. 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 and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in <1% of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.

Paediatric population

The safety profile of SPRYCEL administered as single-agent therapy in paediatric patients with chronic phase Ph+ CML was comparable to the safety profile in adults.

The safety profile of SPRYCEL administered in combination with chemotherapy in paediatric patients with Ph+ ALL was consistent with the known safety profile of SPRYCEL in adults and the expected effects of chemotherapy, with the exception of a lower pleural effusion rate in paediatric patients as compared to adults.

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

In the paediatric ALL studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults, within the context of an acute leukaemia patient receiving a background chemotherapy regimen.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Dasatinib Plasma Concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg SPRYCEL once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib C_{max} and AUC by four- and five-fold, respectively. Concomitant use of

SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.1)]*.

7.2 Drugs That May Decrease Dasatinib Plasma Concentrations

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

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

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. In a study of 24 healthy subjects, administration of a single 50-mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and C_{max} of dasatinib by 61% and 63%, respectively. In another study of 14 healthy subjects, administration of a single 100-mg dose of SPRYCEL 22 hours following a 4-day, 40-mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C_{max} of dasatinib by 42%. The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

7.3 Drugs That May Have Their Plasma Concentration Altered By Dasatinib

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

SPRYCEL can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of SPRYCEL in pregnant women. However, there have been reports of spontaneous abortion and fetal and infant anomalies from women who have taken SPRYCEL during pregnancy.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. Sexually active male or female patients of child bearing potential taking SPRYCEL should use adequate contraception. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus. 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. 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, clavicle), reduced ossification (sternum; thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia.

8.2 Nursing Mothers

It is unknown whether SPRYCEL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SPRYCEL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

Ph+ CML in Chronic Phase

The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML *[see Clinical Studies (13)]*. There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported *[see Warnings and Precautions (5.10)]*.

Ph+ ALL

The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported.

The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects *[see Adverse Reactions (6) and Clinical Studies (13)]*.

Monitor bone growth and development in pediatric patients *[see Warnings and Precautions (5.10)]*.

Pediatric Patients with Difficulty Swallowing Tablets
Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. The exposure for dispersed tablets was 36% lower as compared to intact tablets in pediatric patients *[see Clinical Pharmacology (11)]*. Due to the limited available clinical data, it is unclear whether dispersing SPRYCEL tablets significantly alters the safety and/or efficacy of SPRYCEL.

8.4 Geriatric Use

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. No differences in confirmed Complete Cytogenetic Response (cCCyR) and MMR were observed between older and younger patients. 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, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease, and should be monitored closely.

8.5 Hepatic Impairment

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

No dosage adjustment is necessary in patients with hepatic impairment *[see Clinical Pharmacology (11)]*. Caution is recommended when administering SPRYCEL to patients with hepatic impairment.

8.6 Renal Impairment

No clinical studies were conducted with SPRYCEL in patients with decreased renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine concentration >3 times the upper limit of the normal range, and 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). 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.

9 OVERDOSAGE

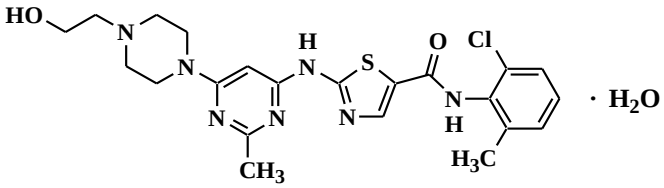
Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6)]*, patients who

ingest more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

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

10 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



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

11 CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Absorption

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

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

Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL.

Metabolism

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

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

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

Elimination

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

Effects Gender

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

Paediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m^2 to 120 mg/m^2 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/m^2, 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.

The bioavailability of dispersed tablets in pediatric patients was estimated to be 36% lower than that of intact tablets.

Hepatic Impairment

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

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

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-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 generally equivalent to the human exposure at the recommended range of starting doses from 100 mg to 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and of prostate adenoma in low-dose males was noted. The relevance of the findings from the rat carcinogenicity study for humans is not known.

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

The effects of dasatinib on male and female fertility have not been studied. However, results of repeat-dose toxicity studies in multiple species indicate the potential for dasatinib to impair reproductive function and fertility. Effects evident in male animals included reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

13 CLINICAL STUDIES

Four single-arm, uncontrolled, open-label Phase 2 clinical studies were conducted to determine the safety and efficacy of dasatinib in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib. One randomized non-comparative study was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose was 70 mg dasatinib twice daily. Dose modifications were allowed for improving activity or management of toxicity [see Dosage and Administration (2)].

Two randomised, open-label Phase 3 studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. In addition, one open-label, randomised, comparative Phase 3 study was conducted in adult patients with newly diagnosed chronic phase CML.

The efficacy of dasatinib is based on haematological and cytogenetic response rates.

Durability of response and estimated survival rates provide additional evidence of dasatinib clinical benefit.

A total of 2,712 patients were evaluated in clinical studies; of these 23% were ≥65 years of age and 5% were ≥75 years of age.

Chronic Phase CML - Newly Diagnosed

An international open-label, multicenter, randomised, comparative Phase 3 study was conducted in adult patients with newly diagnosed chronic phase CML. Patients were randomised to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. The primary endpoint was the rate of confirmed complete cytogenetic response (cCCyR) within 12 months. Secondary endpoints included time in cCCyR (measure of durability of response), time to cCCyR, major molecular response (MMR) rate, time to MMR, progression free survival (PFS) and overall survival (OS). Other relevant efficacy results included CCyR and complete molecular response (CMR) rates. The study is ongoing.

A total of 519 patients were randomised to a treatment group: 259 to SPRYCEL and 260 to imatinib. Baseline characteristics were well balanced between the two treatment groups with respect to age (median age was 46 years for the SPRYCEL group and 49 years for the imatinib group with 10% and 11% of patients 65 years of age or older, respectively), gender (women 44% and 37%, respectively), and race (Caucasian 51% and 55%; Asian 42% and 37%, respectively). 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 randomised to the SPRYCEL group and 81% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation within 12 months due to disease progression occurred in 3% of SPRYCEL-treated patients and 5% of imatinib-treated patients.

With a minimum of 60 months follow-up, 60% of patients randomised to the SPRYCEL group and 63% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation within 60 months due to disease progression occurred in 11% of SPRYCEL-treated patients and 14% of imatinib-treated patients.

Efficacy results are presented in Table 10. A statistically significantly greater proportion of patients in the SPRYCEL group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of SPRYCEL was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

Table 10: Efficacy Results in a Phase III study of Newly Diagnosed Patients with Chronic Phase CML

	SPRYCEL n= 259	imatinib n= 260	p-value
	Response rate (95% CI)		
Cytogenetic response			
within 12 months			
cCCyR[a]	76.8% (71.2–81.8)	66.2% (60.1–71.9)	p <0.007*
CCyR[b]	85.3% (80.4-89.4)	73.5% (67.7-78.7)	—
within 24 months			
cCCyR[a]	80.3%	74.2%	—
CCyR[b]	87.3%	82.3%	—
within 36 months			
cCCyR[a]	82.6%	77.3%	—
CCyR[b]	88.0%	83.5%	—
within 48 months			
cCCyR[a]	82.6%	78.5%	—
CCyR[b]	87.6%	83.8%	—
within 60 months			
cCCyR[a]	83.0%	78.5%	—
CCyR[b]	88.0%	83.8%	—
Major Molecular Response[c]			
12 months	52.1% (45.9–58.3)	33.8% (28.1–39.9)	p <0.00003*
24 months	64.5% (58.3–70.3)	50% (43.8–56.2)	—
36 months	69.1% (63.1–74.7)	56.2% (49.9–62.3)	—
48 months	75.7% (70.0–80.8)	62.7% (56.5–68.6)	—
60 months	76.4%(70.8–81.5)	64.2% (58.1–70.1)	p = 0.0021
	Hazard Ratio (HR)		
	within 12 months (99.99% CI)		
Time to cCCyR	1.55 (1.0-2.3)		p <0.0001*
Time to MMR	2.01 (1.2-3.4)		p <0.0001*
Durability of cCCyR	0.7 (0.4-1.4)		p <0.035
	within 24 months (95% CI)		
Time to cCCyR	1.49 (1.22–1.82)		—
Time to MMR	1.69 (1.34–2.12)		—
Durability of cCCyR	0.77 (0.55–1.10)		—

	within 36 months (95% CI)	
Time to cCCyR	1.48 (1.22–1.80)	—
Time to MMR	1.59 (1.28–1.99)	—
Durability of cCCyR	0.77 (0.53–1.11)	—
	within 48 months (95% CI)	
Time to cCCyR	1.45 (1.20–1.77)	—
Time to MMR	1.55 (1.26–1.91)	—
Durability of cCCyR	0.81 (0.56–1.17)	—
	within 60 months (95% CI)	
Time to cCCyR	1.46 (1.20–1.77)	p=0.0001
Time to MMR	1.54 (1.25–1.89)	p <0.0001
Durability of cCCyR	0.79 (0.55–1.13)	p=0.1983

[a] Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart).

[b] Cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation.

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

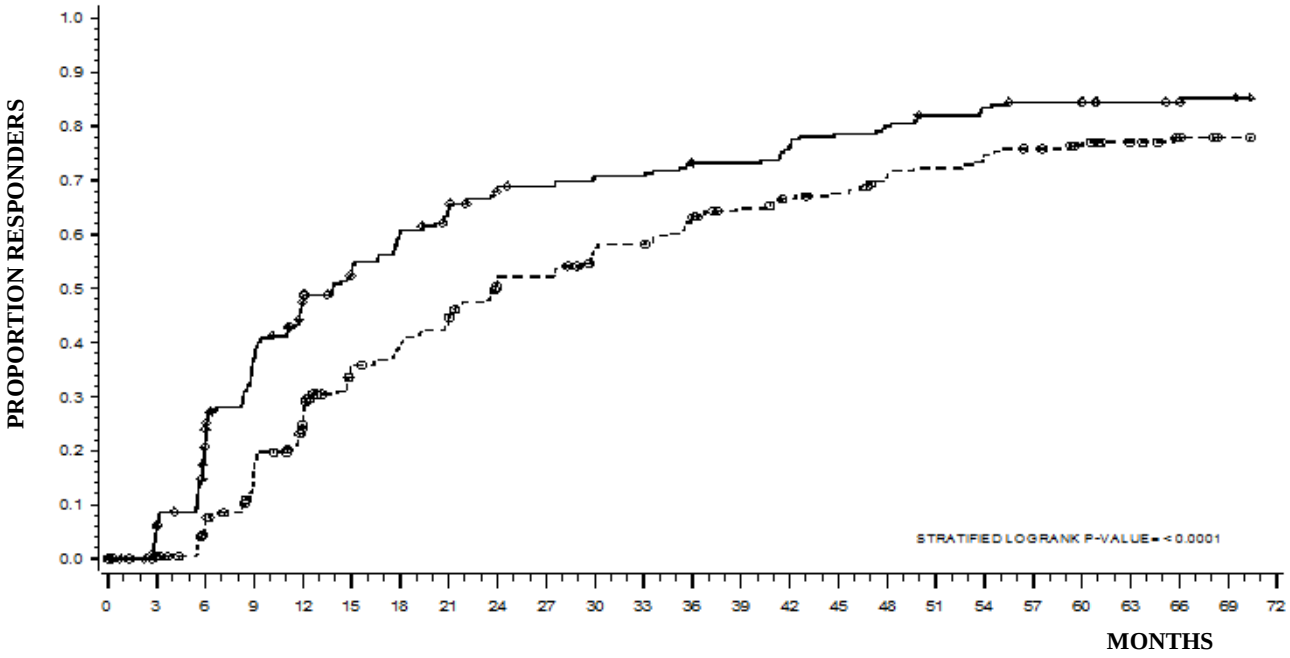
[*] Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.

CI = confidence interval

After 60 months of follow-up, median time to cCCyR was 3.1 months in the SPRYCEL group and 5.8 months in the imatinib group in patients with a confirmed CCyR. Median time to MMR after 60 months follow-up was 9.3 months in the SPRYCEL group and 15.0 months in the imatinib group in patients with a MMR. These results are consistent with those seen at 12, 24 and 36 months.

The time to MMR is displayed graphically in Figure 1. The time to MMR was consistently shorter in SPRYCEL-treated patients compared with imatinib-treated patients.

Figure 1: Kaplan-Meier estimate of time to major molecular response (MMR)



___ Dasatinib
◊◊◊ Censored

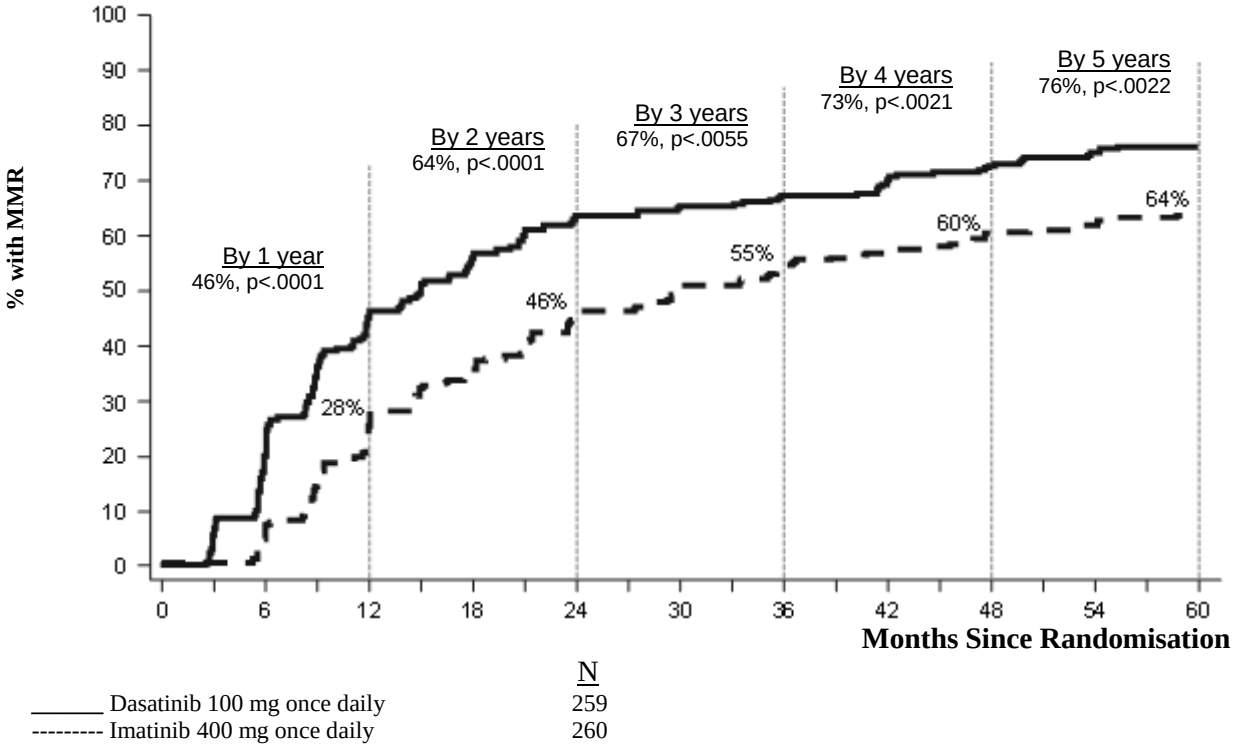
------ Imatinib
⊙⊙⊙ Censored

GROUP	# RESPONDERS / # RANDOMIZED	HAZARD RATIO (95% CI)
DASATINIB	198/259	
IMATINIB	167/260	
DASATINIB OVER IMATINIB		1.54(1.25 - 1.89)

The rates of cCCyR in the SPRYCEL and imatinib treatment groups, respectively, within 3 months (54% and 30%), 6 months (70% and 56%), 9 months (75% and 63%), 24 months (80% and 74%), 36 months (83% and 77%), 48 months (83% and 79%) and 60 months (83% and 79%) were consistent with the primary endpoint. The rates of MMR in the SPRYCEL and imatinib treatment groups, respectively, within 3 months (8% and 0.4%), 6 months (27% and 8%), 9 months (39% and 18%), 12 months (46% and 28%), 24 months (64% and 46%), 36 months (67% and 55%), 48 months (73% and 60%) and 60 months (76% and 64%) were also consistent with the primary endpoint.

MMR rates by specific timepoint are displayed graphically in Figure 2. Rates of MMR were consistently higher in dasatinib-treated patients compared with imatinib-treated patients.

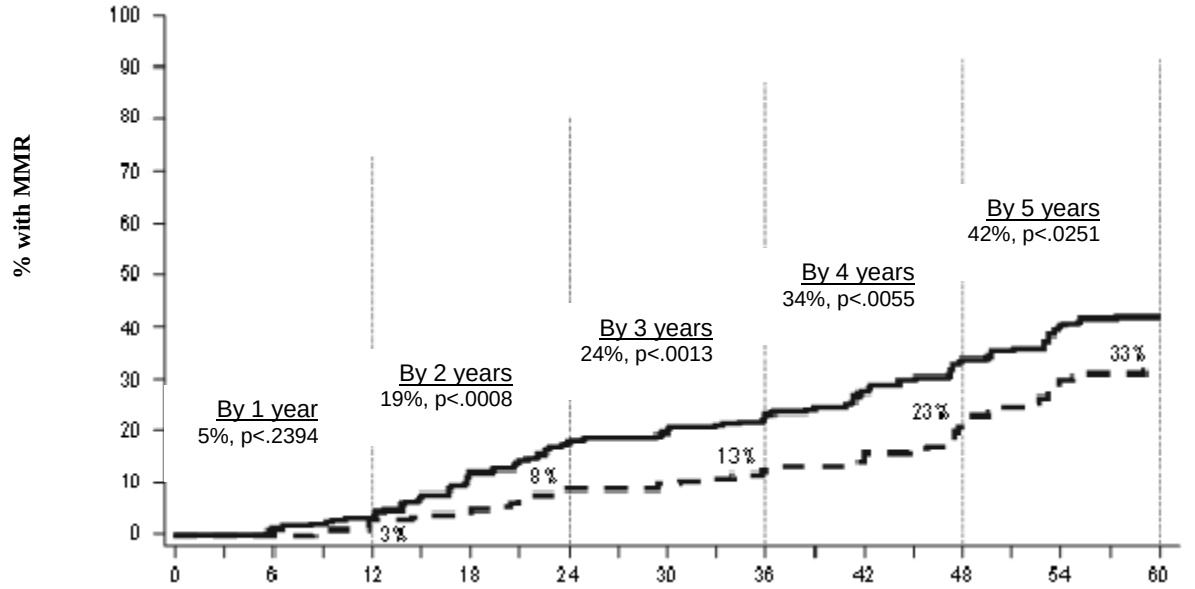
Figure 2: MMR Rates Over Time - All Randomised Patients in a Phase 3 Study of Newly Diagnosed Patients with Chronic Phase CML)



The proportion of patients achieving BCR-ABL ratio of ≤0.01% (4-log reduction) at any time was higher in the SPRYCEL group compared to the imatinib group (54.1% versus 45.0%). The proportion of patients achieving BCR-ABL ratio of ≤0.0032% (4.5-log reduction) at any time was higher in the SPRYCEL group compared to the imatinib group (44% versus 34%).

MR4.5 rates over time is displayed graphically in Figure 3. Rates of MR4.5 over time was consistently higher in SPRYCEL-treated patients compared with imatinib-treated patients.

Figure 3: MR4.5 Rates Over Time - All Randomised Patients in a Phase 3 Study of Newly Diagnosed Patients with Chronic Phase CML



	N
_____ Dasatinib 100 mg once daily	259
--------- Imatinib 400 mg once daily	260

The rate of MMR at any time in each risk group determined by Hasford score was higher in the SPRYCEL group compared with the imatinib group (low risk: 90% and 69%; intermediate risk: 71% and 65%; high risk: 67% and 54%, respectively).

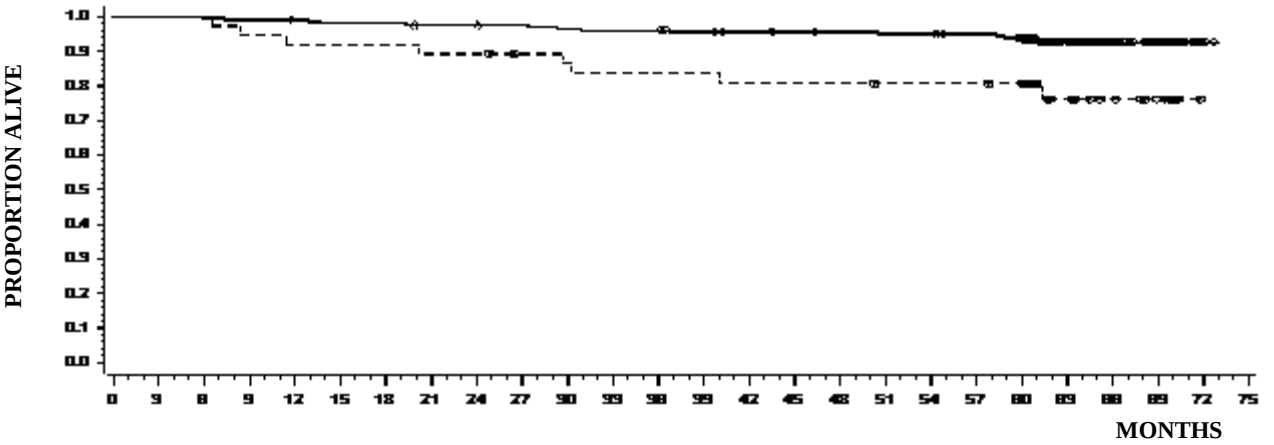
In an additional analysis, more SPRYCEL-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels ≤ 10% at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 11.

Table 11: Dasatinib Patients with BCR-ABL ≤ 10% and > 10% at 3 Months

Dasatinib N = 235	**Patients with BCR-ABL ≤ 10% at 3 Months**	**Patients with BCR-ABL > 10% at 3 Months**
Number of Patients (%)	198 (84.3)	37 (15.7)
Transformation at 60 months, n/N (%)	6/198 (3.0)	5/37 (13.5)
Rate of PFS at 60 Months (95% CI)	92.0% (89.6, 95.2)	73.8% (52.0, 86.8)
Rate of OS at 60 Months (95% CI)	93.8% (89.3, 96.4)	80.6% (63.5, 90.2)

The OS rate by specific timepoint is displayed graphically in Figure 4. Rate of OS was consistently higher in dasatinib treated patients who achieved BCR-ABL level ≤ 10% at 3 months than those who did not.

Figure 4: Landmark Plot for Overall Survival for Dasatinib by BCR-ABL Level (≤ 10% or > 10%) at 3 Months in a Phase 3 Study of Newly Diagnosed Patients with Chronic Phase CML



Patients at Risk

<=10%	198	198	197	196	195	193	193	191	191	190	188	187	187	184	182	181	180	179	179	177	171	96	54	29	3	0
>10%	37	37	37	35	34	34	34	33	33	31	30	29	29	29	28	28	28	27	27	27	26	15	10	6	0	0

___≤10% ◊◊◊ Censored

------ >10% ⊙⊙⊙ Censored

GROUP	# DEATHS / # Land Patient	MEDIAN (95% CI)	HAZARD RATIO (95% CI)
≤10%	14/198	.(. - .)	
>10%	8/37	.(. - .)	
			0.29 (0.12 - 0.69)

Disease progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR, partial CyR or CCyR, progression to accelerated phase or blast phase, or death. The estimated 60-month PFS rate was 88.9% (CI: 84%–92.4%) and 90.9% (CI: 87.1%–94.6%) for the dasatinib and imatinib treatment groups, respectively. At 60 months, transformation to accelerated or blast phase occurred in fewer SPRYCEL-treated patients (n=8; 3.1%) compared with imatinib-treated patients (n=15; 5.8%). The estimated 60 -month survival rates for dasatinib and imatinib-treated patients were 88.9% (CI: 84%–92.4%) and 89.2% (CI: 84.3%–92.7%), respectively. There was no difference in OS (HR 1.01, 95% CI: 0.58-1.73, p= 0.9800) and PFS (HR 1.00, 95% CI: 0.58-1.72, p = 0.9998) between SPRYCEL and imatinib.

In patients who report disease progression or discontinue dasatinib or imatinib therapy, BCR-ABL sequencing was performed on blood samples from patients where these are available. Similar rates of mutation were observed in both the treatment arms. The mutations detected among the dasatinib-treated patients were T315I, F3171/L, and V299L. A different spectrum of mutation was detected in the imatinib-treatment arm. Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

Chronic Phase CML - Resistance or intolerance to prior imatinib therapy

Two clinical studies were conducted in patients resistant or intolerant to imatinib; the primary efficacy endpoint in these studies was Major Cytogenetic Response (MCyR).

1- An open-label, randomised, non-comparative multicenter study was conducted in patients who failed initial treatment with 400 or 600 mg imatinib. They were randomised (2:1) to either dasatinib (70 mg twice daily) or imatinib (400 mg twice daily). Crossover to the alternative treatment arm was allowed if patients showed evidence of disease progression or intolerance that could not be managed by dose modification. The primary endpoint was MCyR at 12 weeks. Results are available for 150 patients: 101 were randomised to dasatinib and 49 to imatinib (all imatinib resistant). The median time from diagnosis to randomisation was 64 months in the dasatinib group and 52 months in the imatinib group. All patients were extensively pretreated. Prior complete haematologic response (CHR) to imatinib was achieved in 93% of the overall patient population. A prior MCyR to imatinib was achieved in 28% and 29% of the patients in the dasatinib and imatinib arms, respectively.

Median duration of treatment was 23 months for dasatinib (with 44% of patients treated for >24 months to date) and 3 months for imatinib (with 10% of patients treated for >24 months to date). Ninety-three percent of patients in the dasatinib arm and 82% of patients in the imatinib arm achieved a CHR prior to crossover.

At 3 months, a MCyR occurred more often in the dasatinib arm (36%) than in the imatinib arm (29%). Notably, 22% of patients reported a complete cytogenetic response (CCyR) in the dasatinib arm while only 8% achieved a CCyR in the imatinib arm. With longer treatment and follow-up (median of 24 months), MCyR was achieved in 53% of the dasatinib-treated patients (CCyR in 44%) and 33% of the imatinib-treated patients (CCyR in 18%) prior to crossover. Among patients who had received imatinib 400 mg prior to study entry, MCyR was achieved in 61% of patients in the dasatinib arm and 50% in the imatinib arm.

Based on the Kaplan-Meier estimates, the proportion of patients who maintained MCyR for 1 year was 92% (95% CI: [85%–100%]) for dasatinib (CCyR 97%, 95% CI: [92%–100%]) and 74% (95% CI: [49%–100%]) for imatinib (CCyR 100%). The proportion of patients who maintained MCyR for 18 months was 90% (95% CI: [82%–98%]) for dasatinib (CCyR 94%, 95% CI: [87%–100%]) and 74% (95% CI: [49%–100%]) for imatinib (CCyR 100%).

Based on the Kaplan-Meier estimates, the proportion of patients who had progression-free survival (PFS) for 1 year was 91% (95% CI: [85%–97%]) for dasatinib and 73% (95% CI: [54%–91%]) for imatinib. The proportion of patients who had PFS at 2 years was 86% (95% CI: [78%–93%]) for dasatinib and 65% (95% CI: [43%–87%]) for imatinib.

A total of 43% of the patients in the dasatinib arm, and 82% in the imatinib arm had treatment failure, defined as disease progression or crossover to the other treatment (lack of response, intolerance of study medicinal product, etc.).

The rate of major molecular response (defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples) prior to crossover was 29% for dasatinib and 12% for imatinib.

2- An open-label, single-arm, multicenter study was conducted in patients resistant or intolerant to imatinib (ie. patients who experienced significant toxicity during treatment with imatinib that precluded further treatment).

A total of 387 patients received dasatinib 70 mg twice daily (288 resistant and 99 intolerant). The median time from diagnosis to start of treatment was 61 months. The majority of the patients (53%) had received prior imatinib treatment for more than 3 years. Most resistant patients (72%) had received >600 mg imatinib. In addition to imatinib, 35% of patients had received prior cytotoxic chemotherapy, 65% had received prior interferon, and 10% had received a prior stem cell transplant. Thirty-eight percent of patients had baseline mutations known to confer imatinib resistance. Median duration of treatment on dasatinib was 24 months with 51% of patients treated for >24 months to date. Efficacy results are reported in Table 14. MCyR was achieved in 55% of imatinib-resistant patients and 82% of imatinib-intolerant patients. With a minimum of 24 months follow-up, 21 of the 240 patients who had achieved a MCyR had progressed and the median duration of MCyR had not been reached.

Based on the Kaplan-Meier estimates, 95% (95% CI: [92%–98%]) of the patients maintained MCyR for 1 year and 88% (95% CI: [83%–93%]) maintained MCyR for 2 years. The proportion of patients who maintained CCyR for 1 year was 97% (95% CI: [94%–99%]) and for 2 years was 90% (95% CI: [86%–95%]). Forty-two percent of the imatinib-resistant patients with no prior MCyR to imatinib (n=188) achieved a MCyR with dasatinib.

There were 45 different BCR-ABL mutations in 38% of patients enrolled in this study. Complete haematologic response or MCyR was achieved in patients harbouring a variety of BCR-ABL mutations associated with imatinib resistance except T315I. The rates of MCyR at 2 years were similar whether patients had any baseline BCR-ABL mutation, P-loop mutation, or no mutation (63%, 61% and 62%, respectively).

Among imatinib-resistant patients, the estimated rate of PFS was 88% (95% CI: [84%–92%]) at 1 year and 75% (95% CI: [69%–81%]) at 2 years. Among imatinib-intolerant patients, the estimated rate of PFS was 98% (95% CI: [95%–100%]) at 1 year and 94% (95% CI: [88%–99%]) at 2 years.

The rate of major molecular response at 24 months was 45% (35% for imatinib-resistant patients and 74% for imatinib-intolerant patients).

Accelerated Phase CML

An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 174 patients received dasatinib 70 mg twice daily (161 resistant and 13 intolerant to imatinib). The median time from diagnosis to start of treatment was 82 months. Median duration of treatment on dasatinib was 14 months with 31% of patients treated for >24 months to date. The rate of major molecular response (assessed in 41 patients with a CCyR) was 46% at 24 months. Further efficacy results are reported in Table 14.

Myeloid Blast Phase CML

An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 109 patients received dasatinib 70 mg twice daily (99 resistant and 10 intolerant to imatinib). The median time from diagnosis to start of treatment was 48 months. Median duration of treatment on dasatinib was 3.5 months with 12% of patients treated for >24 months to date. The rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months. Further efficacy results are reported in Table 14.

Lymphoid Blast Phase CML and Ph+ ALL

An open-label, single-arm, multicenter study was conducted in patients with lymphoid blast phase CML or Ph+ ALL who were resistant or intolerant to prior imatinib therapy. A total of 48 patients with lymphoid blast CML received dasatinib 70 mg twice daily (42 resistant and 6 intolerant to imatinib). The median time from diagnosis to start of treatment was 28 months. Median duration of treatment on dasatinib was 3 months with 2% treated for >24 months to date. The rate of major molecular response (all 22 treated patients with a CCyR) was 50% at 24 months. In addition, 46 patients with Ph+ ALL received dasatinib 70 mg twice daily (44 resistant and 2 intolerant to imatinib). The median time from diagnosis to start of treatment was 18 months. Median duration of treatment on dasatinib was 3 months with 7% of patients treated for >24 months to date. The rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months. Further efficacy results are reported in Table 12. Of note, major haematologic responses (MaHR) were achieved quickly (most within 35 days of first dasatinib administration for patients with lymphoid blast CML, and within 55 days for patients with Ph+ ALL).

Table 12: Efficacy in Phase 2 SPRYCEL Single-Arm Clinical Studies[a]

	Chronic (n= 387)	Accelerated (n= 174)	Myeloid Blast (n= 109)	Lymphoid Blast (n= 48)	Ph+ ALL (n= 46)
Haematologic Response Rate[b] (%)					
MaHR (95% CI)	n/a	**64% (57-72)**	**33% (24-43)**	**35% (22-51)**	**41% (27-57)**
CHR (95% CI)	**91% (88-94)**	50% (42-58)	26% (18-35)	29% (17-44)	35% (21-50)
NEL (95% CI)	n/a	14% (10-21)	7% (3-14)	6% (1-17)	7% (1-18)
Duration of MaHR (%; Kaplan-Meier Estimates)					
1 Year	n/a	79% (71-87)	71% (55-87)	29% (3-56)	32% (8-56)
2 Years	n/a	60% (50-70)	41% (21-60)	10% (0-28)	24% (2-47)
Cytogenetic Response[c] (%)					
MCyR (95% CI)	**62% (57-67)**	40% (33-48)	34% (25-44)	52% (37-67)	57% (41-71)
CCyR (95% CI)	54% (48-59)	33% (26-41)	27% (19-36)	46% (31-61)	54% (39-69)
Survival (%; Kaplan-Meier Estimates)					
Progression-Free					
1 Year	91% (88-94)	64% (57-72)	35% (25-45)	14% (3-25)	21% (9-34)
2 Years	80% (75-84)	46% (38-54)	20% (11-29)	5% (0-13)	12% (2-23)
Overall					
1 Year	97% (95-99)	83% (77-89)	48% (38-59)	30% (14-47)	35% (20-51)
2 Years	94% (91-97)	72% (64-79)	38% (27-50)	26% (10-42)	31% (16-47)

Note: Data described in this table are from studies using a starting dose of 70 mg twice daily. See DOSAGE AND ADMINISTRATION for the recommended starting dose.

[a] Numbers in bold font are the results of primary endpoints.

[b] Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response (MaHR) = complete haematologic response (CHR) + no evidence of leukaemia (NEL).

CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥1,000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥500/mm^3 and <1,000/mm^3, or platelets ≥20,000/mm^3 and ≤100,000/mm^3.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%-35%). MCyR (0%-35%) combines both complete and partial responses.

n/a = not applicable. CI = confidence interval. ULN = upper limit of normal range.

The outcome of patients with bone marrow transplantation after dasatinib treatment has not been fully evaluated.

Phase 3 clinical studies in patients with CML in chronic, accelerated, or myeloid blast phase, and Ph+ ALL who were resistant or intolerant to imatinib

Two randomised, open-label studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. Results described below are based on a minimum of 2 years and 7 years follow-up after the start of dasatinib therapy.

1- A randomized, open-label study was conducted in patients with chronic phase CML, whose disease was resistant to or who were intolerant to imatinib, to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the study.

The primary endpoint was MCyR in imatinib-resistant patients. The main secondary endpoint was MCyR by total daily dose level in the imatinib-resistant patients. Other secondary endpoints included duration of MCyR, PFS, and overall survival. A total of 670 patients, of whom 497 were imatinib resistant, were randomized to the SPRYCEL 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. The median duration of treatment for all patients still on therapy with a minimum of 5 years of follow-up (n=205) was 59 months (range 28-66 months). Median duration of treatment for all patients at 7 years of follow-up was 29.8 months (range <1 - 92.9 months).

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% CI [-6.8%–10.6%]); however, the 100 mg once daily regimen demonstrated improved safety and tolerability Efficacy results are presented in Tables 13 and 14.

Table 13: Efficacy of SPRYCEL in Phase 3 Dose-Optimisation Study: Imatinib Resistant or Intolerant Chronic Phase CML (2-year results)[a]

All Patients	**n=167**
Imatinib-Resistant Patients	**n=124**
Hematologic Response Rate[b] (%) (95% CI)	
CHR	**92% (86–95)**
Cytogenetic Response[c] (%) (95% CI)	
MCyR	
All Patients	**63% (56–71)**
Imatinib-Resistant Patients	**59% (50–68)**
CCyR	
All Patients	**50% (42–58)**
Imatinib-Resistant Patients	**44% (35–53)**
Major Molecular Response in Patients achieving CCyR[d] (%) (95% CI)	
All Patients	**69% (58–79)**
Imatinib-Resistant Patients	**72% (58–83)**

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

[b] Hematologic response criteria (all responses confirmed after 4 weeks): Complete hematologic response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm3TP, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

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

Table 14: Long Term Efficacy of SPRYCEL in Phase 3 Dose Optimisation Study: Imatinib Resistant or Intolerant Chronic Phase CML Patients [a]

	Minimum Follow-up Period			
	1 year	**2 years**	**5 years**	**7 years**
Major Molecular Response				
All patients	NA	37% (57/154)	44% (71/160)	46% (73/160)
Imatinib-resistant patients	NA	35% (41/117)	42% (50/120)	43% (51/120)
Imatinib-intolerant patients	NA	43% (16/37)	53% (21/40)	55% (22/40)
Progression-Free Survival[b]				
All patients	90% (86, 95)	80% (73, 87)	51% (41, 60)	42% (33, 51)
Imatinib-resistant patients	88% (82, 94)	77% (68, 85)	49% (39, 59)	39% (29, 49)
Imatinib-intolerant patients	97% (92, 100)	87% (76, 99)	56% (37, 76)	51% (32, 67)
Overall Survival				
All patients	96% (93, 99)	91% (86, 96)	78% (72, 85)	65% (56, 72)
Imatinib-resistant patients	94% (90, 98)	89% (84, 95)	77% (69, 85)	63% (53, 71)
Imatinib-intolerant patients	100% (100, 100)	95% (88, 100)	82% (70, 94)	70% (52, 82)

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

[b] Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, confirmed AP/BP disease or death. PFS was analysed on an intent-to-treat principle and patients were followed to events including subsequent therapy.

Based on the Kaplan-Meier estimates, the proportion of patients treated with dasatinib 100 mg once daily who maintained MCyR for 18 months was 93% (95% CI: [88%-98%]).

Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77% and CCyR in 67%.

2- A randomized, open-label study was conducted in patients with advanced phase CML and Ph+ ALL, whose disease was resistant to or who were intolerant to imatinib, to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary endpoint was MaHR. A total of 611 patients were randomized to either the SPRYCEL 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range 0.03–31 months).

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [−7.1%–8.7%]), however, the 140 mg once daily regimen demonstrated improved safety and tolerability. Response rates are presented in Table 15.

Table 15: Efficacy of SPRYCEL in Phase III Dose-Optimisation study: Advanced Phase CML and Ph+ ALL (2 Year Results)[a]

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

[a] Results reported in recommended starting dose of 140 mg once daily (see section 2).

[b] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response (MaHR) = complete hematologic response (CHR) + no evidence of leukaemia (NEL).

CHR: WBC ≤ institutional ULN, ANC ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥ 500/mm^3 and < 1,000/mm^3, or platelets ≥ 20,000/mm^3 and ≤ 100,000/mm^3.

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

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

In patients with accelerated phase CML treated with the 140 mg regimen, the median duration of MaHR and the median overall survival was not reached and the median PFS was 25 months.

In patients with myeloid blast phase CML treated with the 140 mg once daily regimen, the median duration of MaHR was 8 months; the median PFS was 4 months, and the median overall survival was 8 months. In patients with lymphoid blast phase CML treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months; the median PFS was 5 months, and the median overall survival was 11 months.

In patients with Ph+ ALL treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months, the median PFS was 4 months, and the median overall survival was 7 months.

CML in Paediatric 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 (NCT00306202) and an open-label, non-randomized, single-arm trial (NCT00777036), 51 patients (exclusively from the single-arm trial) had newly diagnosed 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/m^2 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 18.

Table 16 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 16: Efficacy of SPRYCEL in pediatric patients with CML-CP Cumulative response over time by minimum follow-up period

	3 months	6 months	12 months	24 months
CCyR (95% CI)				
Newly diagnosed (N = 51)[a]	43.1% (29.3, 57.8)	66.7% (52.1, 79.2)	96.1% (86.5, 99.5)	96.1% (86.5, 99.5)
Prior imatinib (N = 46)[b]	45.7% (30.9, 61.0)	71.7% (56.5, 84.0)	78.3% (63.6, 89.1)	82.6% (68.6, 92.2)
MCyR (95% CI)				
Newly diagnosed (N = 51)[a]	60.8% (46.1, 74.2)	90.2% (78.6, 96.7)	98.0% (89.6, 100)	98.0% (89.6, 100)
Prior imatinib (N = 46)[b]	60.9% (45.4, 74.9)	82.6% (68.6, 92.2)	89.1% (76.4, 96.4)	89.1% (76.4, 96.4)
MMR (95% CI)				
Newly diagnosed (N = 51)[a]	7.8% (2.2, 18.9)	31.4% (19.1, 45.9)	56.9% (42.2, 70.7)	74.5% (60.4, 85.7)
Prior imatinib (N = 46)[b]	15.2% (6.3, 28.9)	26.1% (14.3, 41.1)	39.1% (25.1, 54.6)	52.2% (36.9, 67.1)

[a] Patients from Phase II paediatric study of newly diagnosed CML-CP receiving oral tablet formulation
[b] Patients from Phase I and Phase II paediatric studies of imatinib-resistant or intolerant CML-CP 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 0.03+ 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 the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.4

to 86.9+ 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/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/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/intolerant CP-CML patients.

The median time to response for MCyR was 3.0 months (95% CI: 2.8 months, 4.3 months) in the newly diagnosed treatment-naive CP-CML patients. The median time to response for CCyR was 5.5 months (95% CI: 3.0 months, 5.7 months) in the newly diagnosed treatment-naive CP-CML patients. The median time to response for MMR was 8.9 months (95% CI: 6.2 months, 11.7 months) in the newly diagnosed treatment-naïve 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.

Ph+ ALL in Pediatric patients with ALL

The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort of Study CA180372 (NCT01460160), a multicenter study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. Eighty-two patients received SPRYCEL tablets at a daily dose of 60 mg/m^2 for up to 24 months, in combination with chemotherapy. The backbone chemotherapy regimen was the AIEOP-BFM ALL 2000 multi-agent chemotherapy protocol.

Patients had a median age of 10.4 years (range 2.6 to 17.9 years) and included 21 patients (25.6%) 2 to 6 years of age, 27 patients (32.9%) 7 to 12 years of age, and 34 patients (41.5%) 13 to 17 years of age. Eighty percent of patients were white, and 55% were male. Thirty-two patients (41%) had a white blood cell count (WBC) of ≥50,000/mcL at diagnosis, and 17 patients (20.7%) had extramedullary disease.

Efficacy was established on the basis of 3-year event-free survival (EFS), defined as the time from the start of SPRYCEL to lack of complete response at the end of the third high risk block, relapse, secondary malignancy, or death from any cause. The 3-year EFS rate for patients on Study CA180372 was 65.1% (95% CI: 53.6, 74.4). At the end of induction, 72 patients (87.8%) had a bone marrow with <5% lymphoblasts, and 77 patients (93.9%) achieved this by the end of consolidation.

The minimal residual disease (MRD) negativity rate assessed by Ig/TCR rearrangement was 74.4% by the end of consolidation in all treated patients. When this rate was based on the 70 patients with evaluable Ig/TCR assessments, the estimate was 87.1%.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 17.

Table 17: SPRYCEL Trade Presentations

Strength	Description	Tablets per Bottle
20 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “527” on the other side	60
50 mg	white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “528” on the other side	60
70 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “524” on the other side	60

14.2 Storage

SPRYCEL tablets should be stored below 30°C.

14.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

SPRYCEL (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 crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed or broken tablets.

15 PATIENT COUNSELING INFORMATION

15.1 Bleeding

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of haemorrhage (unusual bleeding or easy bruising).

15.2 Myelosuppression

Patients should be informed of the possibility of developing low blood cell counts; they should be instructed to report immediately should fever develop, particularly in association with any suggestion of infection.

15.3 Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, or shortness of breath) and to seek medical attention if those symptoms arise.

15.4 Pregnancy

Patients should be informed that dasatinib may cause fetal harm when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.7)]*.

15.5 Gastrointestinal Complaints

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

15.6 Pain

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

15.7 Fatigue

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

15.8 Rash

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

15.9 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.

Marketed by:
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