AUSTRALIAN PRODUCT INFORMATION – SPRYCEL® (DASATINIB)

1 NAME OF THE MEDICINE

Dasatinib.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SPRYCEL film-coated tablets contain 20, 50, 70 or 100 mg of dasatinib.

Dasatinib is a white to off-white powder.

SPRYCEL film-coated tablets contain lactose monohydrate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SPRYCEL film-coated tablets.

The 20 mg tablets are white to off-white, biconvex, round tablets with “BMS” debossed on one side and “527” on the other side.

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

The 70 mg tablets are white to off-white, biconvex, round tablets with “BMS” debossed on one side and “524” on the other side.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SPRYCEL is indicated for the treatment of adults aged 18 years or over with:

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

SPRYCEL is indicated for the treatment of paediatric patients with:

- Ph+ CML in the chronic phase.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Adult Dosage

CML

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

Ph+ ALL

The recommended starting dosage of SPRYCEL for newly diagnosed Ph+ ALL in adults is 100 mg administered orally once daily (QD) or as clinically recommended. SPRYCEL should be taken consistently either in the morning or evening.

The recommended starting dosage of SPRYCEL for adult patients resistant or intolerant to prior therapy is 140 mg/day administered orally once daily (QD). SPRYCEL should be taken consistently either in the morning or the evening.

In clinical studies, treatment with SPRYCEL was continued in the maintenance phase until disease progression or until no longer tolerated by the patient.

Paediatric dosage

Dosing for children is on the basis of body weight. Dasatinib is administered orally once daily in the form of SPRYCEL tablets (20 mg, 50 mg, 70 mg or 100 mg). Recalculate the dose every 3 months based on changes in body weight, or more often if necessary. SPRYCEL tablets are not recommended for patients weighing less than 10 kg. There is no experience with SPRYCEL treatment in children under 1 year of age.

The recommended starting daily dosage of SPRYCEL tablets in paediatric patients is shown in Table 1.

Table 1 Dosage of SPYCEL Tablets for Paediatric Patients

Body Weight (kg)	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

Method of administration

To be administered orally. Tablets must not be crushed, cut or chewed; they should be swallowed whole to maintain dosing consistency and minimize the risk of dermal exposure. Film-coated tablets should not be dispersed, as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet. However, there are additional administration considerations for paediatric patients who have difficulty swallowing tablets whole (see Section 4.4 Special warnings and precautions – Paediatric use).

SPRYCEL can be taken with or without a meal and should be taken consistently either in the morning or the evening. SPRYCEL should not be taken with grapefruit or grapefruit juice (see 4.5 Interactions with other medicines and other forms of interactions).

Treatment duration

In clinical studies, treatment with SPRYCEL in adults with chronic phase CML; accelerated, myeloid or lymphoid blast phase (advanced phase) CML; or Ph+ ALL and in paediatric 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 investigated.

In clinical studies, treatment with SPRYCEL in paediatric patients with Ph+ ALL was administered continuously, added to successive blocks of backbone chemotherapy, for a maximum duration of two years. In patients that receive a subsequent stem cell transplantation, SPRYCEL can be administered for an additional year post-transplantation.

Dose escalation

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

In clinical studies in adult Ph+ ALL patients, dose escalation to 140 mg daily (newly diagnosed patients) or 180 mg once daily (patients on prior therapy) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage.

The following dose escalations shown in Table 2 are recommended in paediatric patients with chronic phase CML who do not achieve a haematologic, cytogenic or molecular response at the recommended time points, per current treatment guidelines, and who tolerate treatment.

Table 2 Dose Escalation for Paediatric Patients with CML

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

Dose escalation is not recommended for paediatric patients with Ph+ ALL, as SPRYCEL is administered in combination with chemotherapy in these patients.

Dose adjustment for adverse reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Tables 3 and 4.

Table 3 Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

Chronic Phase CML or Ph+ ALL (newly diagnosed patients) (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. 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 (patients resistant or intolerant to other therapy (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 Adjustments for Neutropenia and Thrombocytopenia in Paediatric Patients with Chronic Phase CML

	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 leukaemia (marrow aspirate or biopsy).	40 mg	20 mg	**
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.	60 mg	40 mg	20 mg
	70 mg	60 mg	50 mg
	100 mg	80 mg	70 mg
3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose.			

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

For paediatric patients with chronic phase CML, if Grade ≥ 3 neutropenia or thrombocytopenia recurs during complete haematologic response (CHR), SPRYCEL should be interrupted, and may be subsequently resumed at a reduced dose. Temporary dose reductions for intermediate degrees of cytopenia and disease response should be implemented as needed.

For paediatric patients with Ph+ ALL, no dose modification is recommended in cases of haematologic Grade 1 to 4 toxicities. If neutropenia and/or thrombocytopenia result in delay of the next block of treatment by more than 14 days, SPRYCEL should be interrupted and resumed 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, a bone marrow assessment should be performed to assess cellularity and percentage of blasts. If marrow cellularity is <10%, treatment with SPRYCEL should be interrupted until ANC >500/μL (0.5 x 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-haematologic adverse reactions

If a moderate (Grade 2) non-haematologic 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-haematologic 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.

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

For paediatric patients with Ph+ ALL who develop non-haematologic adverse reactions, if needed, one level of dose reduction should be followed, according to the dose reduction recommendations for haematologic adverse reactions that are described above. With the exception of liver function test abnormalities, treatment should be interrupted for cases of Grade ≥3 non-haematologic adverse reactions in paediatric patients with Ph+ ALL, and resumed at a reduced dose when resolved to Grade ≤1. For elevated direct bilirubin over 5 times the institutional upper limit of normal (ULN), treatment should be interrupted until improvement to baseline or Grade ≤1. For elevated AST/ALT over 15 times the institutional ULN, treatment should be interrupted until improvement to baseline or Grade <1. If these liver function test abnormalities recur after re-initiation of treatment with SPRYCEL, the dose should be reduced.

Dose reduction for concomitant use of strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with SPRYCEL should be avoided (see 4.5 Interactions with other medicines and other forms of interactions). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. 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 stop 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.

Special Populations

Elderly population

No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in the elderly (see Section 4.4 Special warnings and precautions – Use in elderly).

Hepatic impairment

Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, caution is recommended when SPRYCEL is administered to patients with hepatic impairment. (see Section 4.4 Special warnings and precautions – Use in hepatic impairment).

Renal impairment

No clinical trials 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 > 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 (see Section 4.4 Special warnings and precautions – Use in renal impairment).

4.3 CONTRAINDICATIONS

Use of SPRYCEL is contraindicated in patients with hypersensitivity to dasatinib or to any other component of SPRYCEL.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myelosuppression

Treatment with SPRYCEL is associated with thrombocytopenia, neutropenia and anaemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML.

In adult patients with advanced phase CML or Ph+ ALL, CBCs should be performed weekly for the first 2 months and then monthly thereafter or as clinically indicated.

In adult and paediatric patients with chronic phase CML, complete blood counts (CBCs) should be performed every two weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated.

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

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily or dose reduction (see Section 4.2 Dose and method of administration – Dose adjustment for adverse reactions and Section 4.4 Special warnings and precautions - Effect on Laboratory Tests). CTC Grade 3 or 4 (severe) cases of anaemia were managed with blood transfusions.

Bleeding

In the pooled population of Phase III studies in patients with chronic phase CML, 5 patients (1%) receiving SPRYCEL at the recommended dose 100 mg daily (n=548) had drug related Grade 3 or 4 haemorrhage. In the pooled population of clinical studies in patients with advanced phase CML or Ph+ ALL, severe (Grade 3 to 5) drug-related CNS haemorrhage, including fatalities, occurred in 1% of patients receiving SPRYCEL at the recommended dose 140 mg daily (n=304). Eight cases were fatal and 6 of them were associated with Common Toxicity Criteria (CTC) Grade 4 thrombocytopenia. Grade

3 or 4 drug-related gastrointestinal haemorrhage, including fatalities, occurred in 6% of patients and generally required treatment interruptions and transfusions. Other cases of Grade 3 or 4 drug-related haemorrhage occurred in 2% of patients treated with dasatinib 140 mg daily dose. Most bleeding reactions in clinical studies were typically associated with Grade 3 or 4 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.

Fluid retention

SPRYCEL is associated with fluid retention. After 5 years of follow-up in the Phase III clinical study in patients with newly diagnosed chronic phase CML (n=258), drug-related Grade 3 or 4 fluid retention was reported in 13 patients (5%) receiving SPRYCEL compared to 2 patients (1%) receiving imatinib (n=258) (see Section 4.8 Adverse effects (undesirable effects)). The cumulative incidence of drug-related pleural effusion (all Grades) in dasatinib-treated subjects increased over time; 7.8% new AEs of pleural effusion occurred in the first year of therapy followed by a smaller, yet consistent increase of ~5% of subjects/year after 24, 36, 48, and 60 months of treatment, respectively. The majority were low grade. In the pooled population of patients with chronic phase CML (n=548), severe (Grade 3 – 4) drug-related fluid retention occurred in 32 (6%) patients receiving SPRYCEL at the 100 mg once daily recommended dose.

In clinical studies in patients with advanced phase CML or Ph+ ALL receiving SPRYCEL at the approved dose 140 mg daily (n=304), Grade 3 or 4 drug-related fluid retention was reported in 8% of patients, including severe pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe congestive heart failure/cardiac dysfunction was reported in 1% of patients. In these patients, severe pulmonary oedema and severe pulmonary hypertension were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion or other fluid retention such as new or worsened dyspnoea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with chest X-ray or additional diagnostic imaging as appropriate. Fluid retention reactions were typically managed with dasatinib dose interruption or reduction and supportive care measures that may include diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy. Dose modification should be considered. While the safety profile of SPRYCEL in the elderly population was similar to that in the younger population, patients aged 65 years and older are more likely to experience pleural effusion, congestive heart failure, gastrointestinal bleeding, and dyspnoea, and should be monitored closely.

Cases of chylothorax have also been reported in patients presenting with pleural effusion. Some cases of chylothorax resolved upon dasatinib discontinuation, interruption or dose reduction but most cases also required additional treatment (see section 4.8).

QT prolongation

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

After 5 years of follow-up in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each of the SPRYCEL (n=258) and imatinib (n=258) treatment groups 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 leukaemia treated with SPRYCEL in Phase II, single-arm 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 2,182 patients with resistance or intolerance to prior imatinib therapy treated with SPRYCEL, 15 (1%) had QT prolongation reported as an adverse reaction. Twenty-one (21) of these patients (1%) experienced a QTcF >500 msec.

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

Cardiac adverse reactions

SPRYCEL was studied in a randomised trial of 519 patients with newly diagnosed CML in chronic phase, which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction (1.9%), pericardial effusion (4.3%), arrhythmias (1.2%), palpitations (1.9%), QT prolongation (0.4%) and myocardial infarction (0.4%) (including fatal) were reported in patients taking SPRYCEL (n=258). Adverse cardiac reactions were more frequent in patients with risk factors or a previous medical history of cardiac disease. Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately.

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

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 co-morbidities 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 dyspnoea and fatigue after initiation of therapy should be evaluated for more common etiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. During this evaluation, guidelines for non-hematologic adverse reactions should be followed (see Section 4.2 Dose and method of administration – Dose adjustment for adverse reactions): 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.

Thrombotic microangiopathy (TMA)

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA), including individual case reports for SPRYCEL (see 4.8 Adverse effects (Undesirable effects)). If laboratory or clinical findings associated with TMA occur in a patient receiving SPRYCEL, treatment with SPRYCEL should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with SPRYCEL should not be resumed.

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.

Severe dermatologic reactions

Individual cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported with the use of SPRYCEL. SPRYCEL should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

Lactose content

SPRYCEL contain 135 mg of lactose monohydrate in a 100 mg daily dose and 189 mg of lactose monohydrate in a 140 mg daily dose.

Effect on growth and development in paediatric patients

In paediatric trials of SPRYCEL in chronic phase CML imatinib-resistant/intolerant paediatric patients and treatment-naive paediatric 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 5.1 Pharmacodynamic properties). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

Hepatotoxicity

SPRYCEL may cause hepatotoxicity as measured by elevations in bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase [see section 4.8 Adverse Effects]. Monitor transaminases at baseline and monthly or as clinically indicated during treatment. Reduce dose, withhold, or permanently discontinue SPRYCEL based on severity. When SPRYCEL is administered in combination with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Monitor hepatic function when SPRYCEL is used in combination with chemotherapy.

Use in hepatic impairment

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see Section 4.2 Dose and method of administration – Special populations and Section 5.2 Pharmacokinetic properties - Special Populations). Due to the limitations of this clinical study, caution is recommended when SPRYCEL is administered to patients with hepatic impairment.

Use in renal impairment

There are currently no clinical studies with SPRYCEL in patients with impaired renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine > 3 times the upper limit of the normal range, and clinical studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range). Dasatinib and its metabolites are minimally excreted via the kidney. Since the renal excretion of unchanged dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

Use in the elderly

Of the 2,712 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.

Patients aged 65 years and older are more likely to experience the commonly reported adverse reactions appetite disturbance (14.5% vs 8.0%), fatigue (27.4% vs 19.7%), pleural effusion (46.2 vs 28.4), cough (13.6% vs 8.4%), and dyspnoea (34.5% vs 17.7%)), and more likely to experience the less frequently reported adverse events abdominal distention (3.9% vs 2.9%), dizziness (7.1% vs 4.6%), lower gastrointestinal haemorrhage (2.4% vs 0.7%), pericardial effusion (7.6% vs 4.9%), congestive heart failure (3.1% vs 0.7%) and weight decrease (7.5% vs 3.7%), and should be monitored closely.

Comparisons based on efficacy are based on limited number of subjects in specific age groups in individual studies, however similar rates of cCCyR and MMR were observed between older and younger patients.

Paediatric use

The safety and efficacy of SPRYCEL in paediatric patients for indications other than Ph+ chronic phase CML and Ph+ ALL (see 5.1 Pharmacological properties – Clinical trials) have not been established.

Paediatric 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 in Study CA180372. The exposure for dispersed tablets was 36% lower as compared to intact tablets in paediatric patients (see Section 5.2 Pharmacokinetic properties – Special populations, Paediatric patients). Due to the limited available clinical data, it is unclear whether dispersing SPRYCEL tablets significantly alters the safety and/or efficacy of SPRYCEL.

Effects on laboratory tests

Haematology and Biochemistry in patients with newly diagnosed chronic phase CML

The comparative frequency of Grade 3 and 4 laboratory abnormalities in patients with newly diagnosed chronic phase CML is presented in Table 5. There were no discontinuations of SPRYCEL therapy due to the biochemical laboratory parameters.

Table 5 CTC Grade 3/4 Laboratory Abnormalities in a Phase III Study of Patients with Newly Diagnosed Chronic Phase

	SPRYCEL n= 258	imatinib n= 258
	Percent (%) of Patients	
Haematology Parameters		
Neutropenia	29	24
Thrombocytopenia	22	14
Anaemia	13	9
Biochemistry Parameters		
Hypophosphataemia	7	31
Hypokalaemia	0	3
Hypocalcaemia	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); anaemia (haemoglobin 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); hypocalcaemia (Grade 3 < 7.0 – 6.0 mg/dl, Grade 4 < 6.0 mg/dl); hypophosphataemia (Grade 3 < 2.0 – 1.0 mg/dl, Grade 4 < 1.0 mg/dl); hypokalaemia (Grade 3 < 3.0 – 2.5 mmol/l, Grade 4 < 2.5 mmol/l).

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

Table 6 shows laboratory findings from clinical trials in adult CML patients with imatinib resistance or intolerance received at 24 months of follow up.

Table 6 CTC Grades 3/4 Laboratory Abnormalities in Studies of Patients with CML Resistant or Intolerant to Prior Imatinib Therapy[a]

	Chronic Phase[b] (n=165)	Accelerated Phase[c] (n=157)	Myeloid Blast Phase[c] (n=74)	Lymphoid Blast Phase[c] (n=33)	Ph+ ALL[c] (n=40)
	Percent (%) of Patients				
Haematology Parameters					
Neutropenia	35	58	77	79	67
Thrombocytopenia	23	63	78	85	72
Anaemia	13	47	74	52	36
Biochemistry Parameters					
Hypophosphataemia	10	13	12	18	16
Hypokalaemia	2	7	11	15	8
Hypocalcaemia	<1	4	9	12	5
Elevated SGPT (ALT)	0	2	5	3	8
Elevated SGOT (AST)	<1	0	4	3	3
Elevated Bilirubin	<1	1	3	6	3
Elevated Creatinine	0	2	8	0	0

[a] Phase III dose optimisation study results reported at 2 years study follow up

[b] CA 180-034 study results in recommended starting dose of 100 mg once daily

[c] CA 180-035 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); anaemia (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); hypocalcaemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphataemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalaemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

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

In patients who experienced Grade 3 or 4 myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of newly diagnosed chronic phase CML patients in the Phase III study and in 5% of patients with resistance or intolerance to prior imatinib therapy in the Phase III study.

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

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 safety profile in adults, within the context of an acute leukaemia patients receiving a background chemotherapy regimen.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors

In vitro, dasatinib is a CYP3A4 substrate. Concomitant use of SPRYCEL and substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving treatment with SPRYCEL, systemic administration of a potent CYP3A4 inhibitor is not recommended. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity (see 4.2 Dose and method of administration).

Drugs that may decrease dasatinib plasma concentrations

CYP3A4 Inducers

Drugs that induce CYP3A4 activity may increase metabolism and decrease dasatinib plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) with SPRYCEL is not recommended. In healthy subjects, the concomitant use of SPRYCEL and rifampicin, a potent CYP3A4 inducer, resulted in a five-fold decrease in dasatinib exposure. In patients for whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Antacids

Non-clinical data demonstrate that the solubility of dasatinib is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with SPRYCEL reduced the AUC of a single dose of SPRYCEL by 55% and the C_{max} by 58%. However, when antacids were administered 2 hours prior to a single dose of SPRYCEL, no relevant changes in SPRYCEL, concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following SPRYCEL. Simultaneous administration of SPRYCEL with antacids should be avoided.

Histamine-2 Antagonists /Proton Pump Inhibitors

Long-term suppression of gastric secretion by Histamine-2 Antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of Histamine-2 Antagonists or proton pump inhibitors with SPRYCEL is not recommended. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of SPRYCEL reduced dasatinib exposure by 61%. The use of antacids should be considered in place of Histamine-2 Antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates

In a study in healthy subjects, a single 100 mg dose of SPRYCEL increased exposure to simvastatin, a known CYP3A4 substrate, by 20%. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL. (see Section 5.1 Pharmacodynamic properties – Mechanism of action).

Other interactions

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

No specific drug interaction studies between dasatinib and chemotherapy regimens routinely used in newly diagnosed Ph+ ALL patients have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study at approximately 1x human clinical exposure (100 or 140 mg dose). However, embryolethality was evident when dams were treated at these doses. Dasatinib caused atrophy/degeneration of the testis in rats and monkeys and an increase in the number of corpora lutea in the ovaries in rats at doses producing plasma exposure levels below or close to that anticipated in patients receiving SPRYCEL therapy. Data evaluating reproductive toxicity in male patients taking SPRYCEL is limited (see Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy).

Use in pregnancy

Pregnancy Category D

Dasatinib may cause fetal harm when administered to a pregnant woman (see Section 4.6 Fertility, pregnancy and lactation – Embryofetal toxicity). In non-clinical studies, at exposure levels that are readily achievable in humans receiving therapeutic doses of 100 mg of SPRYCEL serious embryo fetal toxicity was observed in both pregnant rats and rabbits. Malformations (including skeletal alterations) and fetal death were observed in rats treated with dasatinib.

SPRYCEL is therefore not recommended for use in women who are pregnant or contemplating pregnancy. Women must be advised to avoid becoming pregnant while on therapy. If SPRYCEL 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.

The potential effects of SPRYCEL on sperm have been evaluated in an oral study of fertility and early embryonic development in rats. Dasatinib is not a reproductive toxicant in male rats at clinically relevant exposures (see Section 4.6 Fertility, pregnancy and lactation - Effects on fertility). However, data evaluating reproductive toxicity in male patients taking SPRYCEL are limited.

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

Embryofetal toxicity

Dasatinib can cause fetal harm when administered to a pregnant woman. There have been post-marketing reports of spontaneous abortion and fetal and infant anomalies from women who have taken SPRYCEL during pregnancy.

Use in lactation.

It is unknown whether SPRYCEL is excreted in human milk. Women who are taking SPRYCEL should not breastfeed. In an exploratory peri- and postnatal development study in rats, dasatinib was detectable in the plasma of breast-fed pups with levels 30-40% of the maternal levels. Pleural effusion and deaths were seen in maternally-exposed rat pups, indicating indirect exposure of dasatinib was incompatible with pup survival, even at sub-therapeutic maternal exposure.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SPRYCEL as single-agent therapy

In total, the clinical trial experience for SPRYCEL administered as single-agent therapy represents 2809 patients, of which 2712 were adult and 97 paediatric. In the 2712 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 the subset of 97 paediatric patients with chronic phase CML, the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

The majority of patients treated with SPRYCEL, regardless of dose or schedule, experienced adverse reactions at some time. In the overall population of 2712 SPRYCEL-treated adult subjects, 520 (19%) experience adverse drug reactions leading to treatment discontinuation.

The overall safety profile of SPRYCEL in the paediatric population was similar to that of the adult population, with the exception of no reported pericardial effusion, pleural effusion, pulmonary oedema, or pulmonary hypertension in the paediatric population. Of the 97paediatric patients with chronic phase CML, 1 (1%) experienced adverse reactions leading to treatment discontinuation.

No dedicated clinical trials have been conducted investigating the safety of dastinib in newly diagnosed Ph+ ALL as a primary outcome. The safety profile of SPRYCEL in 4 Phase II clinical trials in newly diagnosed patients with Ph+ ALL, was generally consistent with the safety profile in patients who were resistant or intolerant to prior therapy.

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in clinical trials where SPRYCEL was administered as single-agent therapy. 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations

Common: weight decreased, weight increased

Uncommon: blood creatine phosphokinase increased, gamma-glutamyl transferase increased

Cardiac disorders

Common: congestive heart failure/cardiac dysfunction[c], pericardial effusion, arrhythmia (including tachycardia), palpitations

Uncommon: myocardial infarction (including fatal outcomes), 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

Blood and lymphatic system disorders

Very common: myelosuppression (including anaemia, neutropenia, thrombocytopenia)

Common: febrile neutropenia

Uncommon: lymphadenopathy, lymphopenia

Rare: aplasia pure red cell

Nervous system disorders

Very common: headache

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

Uncommon: CNS bleeding[b], syncope, tremor, amnesia, balance disorder

Rare: cerebrovascular accident, transient ischemic attack, convulsion, optic neuritis, VII[th] nerve paralysis, dementia, ataxia

Eye disorders

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

Uncommon: conjunctivitis, visual impairment, photophobia, lacrimation increased

Ear and labyrinth disorders

Common: tinnitus

Uncommon: hearing loss, vertigo

Respiratory, thoracic and mediastinal disorders

Very common: pleural effusion, dyspnoea

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

Uncommon: bronchospasm, asthma, dysphonia, pulmonary arterial hypertension

Rare: acute respiratory distress syndrome, pulmonary embolism

Gastrointestinal disorders

Very common: diarrhoea, vomiting, nausea, abdominal pain

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

Uncommon: pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastro-oesophageal reflux disease

Rare: protein-losing gastroenteropathy, ileus, pancreatitis acute, anal fistula

Renal and urinary disorders

Uncommon: renal failure, urinary frequency, proteinuria

Rare: renal impairment

Skin and subcutaneous tissue disorders

Very common: skin rash[e]

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

Musculoskeletal and connective tissue disorders

Very common: musculoskeletal pain

Common: arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm

Uncommon: rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis

Rare: epiphyses delayed fusion[g], growth retardation[g]

Metabolism and nutrition disorders

Common: appetite disturbances[a], hyperuricaemia

Uncommon: dehydration, hypoalbuminaemia, hypercholesterolemia, tumour lysis syndrome

Rare: diabetes mellitus

Infections and infestations

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

Common: pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon reports of fatal outcome)

Injury, poisoning, and procedural complications

Common: contusion

Vascular disorders

Very common: haemorrhage[d]

Common: hypertension, flushing

Uncommon: hypotension, thrombophlebitis, thrombosis

Rare: deep vein thrombosis, embolism, livedo reticularis

Not known: thrombotic microangiopathy

General disorders and administration site conditions

Very common: peripheral oedema[g] fatigue, face oedema[h], pyrexia

Common: asthenia, pain, chest pain, generalised oedema[i], chills

Uncommon: malaise, other superficial oedema[j]

Rare: gait disturbance

Immune System Disorders

Uncommon: hypersensitivity (including erythema nodosum)

Rare: anaphylactic shock[k]

Endocrine Disorders

Uncommon: hypothyroidism

Rare: hyperthyroidism, thyroiditis

Hepatobiliary disorders

Uncommon: hepatitis, cholecystitis, cholestasis

Reproductive system and breast disorders

Uncommon: gynecomastia, menstrual disorder

Pregnancy, puerperium and perinatal conditions

Rare: abortion

Psychiatric disorders

Common: depression, insomnia

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

[a] Includes decreased appetite, early satiety, increased appetite

[b] Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

[c] 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.

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

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

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

[g] Includes gravitational oedema, localised oedema, oedema peripheral

[h] includes conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face

[i] includes fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling (reported only in paediatric studies), oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema

[j] includes genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling

[k] Reported only in paediatric studies

SPRYCEL in combination with chemotherapy

Paediatric patients with Ph+ ALL

In Study CA180-372, 82 paediatric patients received SPRYCEL in combination with chemotherapy on a continuous dosing regimen. The median duration of therapy was 23.6 months (range 2.4 to 27.1 months). Of the 82 Ph+ ALL paediatric patients, 2 (2.4%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in Study CA180372 at a frequency of ≥10% are shown in Table 7:

Table 7 Adverse Reactions Reported in ≥10% of Paediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=82)

	Percent (%) of Patients	
Adverse Reaction	**All Grades**	**Grade ¾**
Febrile neutropenia	23	23
Nausea	21	4
Vomiting	18	4
Diarrhea	12	4
Abdominal pain	13	4
Pyrexia	12	6
Fatigue	11	0
Rash	11	0
Headache	11	5

Post marketing Experience

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

Infections and infestations:	hepatitis B reactivation
Cardiac disorders:	atrial fibrillation/atrial flutter[a]
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease, pleural effusion, chylothorax.
Skin and subcutaneous tissue disorders:	Stevens-Johnson syndrome[b]
Renal and urinary disorders:	nephrotic syndrome
Hepatobiliary disorders:	hepatotoxicity

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

[b] 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 medications.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdosage of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since SPRYCEL is associated with severe myelosuppression, patients who ingest more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dasatinib is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus. Dasatinib inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nanomolar or subnanomolar concentrations. Dasatinib also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of kinase's active conformation.

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

Clinical trials

In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

Four single-arm, uncontrolled, open-label Phase II clinical trials were conducted to determine the safety and efficacy of SPRYCEL in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib.

One randomized, comparative trial was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose of SPRYCEL was 70 mg twice daily. Dose modifications were allowed for improving activity or management of toxicity.

Two randomised, open-label Phase III trials were conducted to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. In addition, one open-

label, randomised, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML.

The efficacy of SPRYCEL is based on haematological and cytogenetic response rates. Durability of response and estimated survival rates provide additional evidence of SPRYCEL clinical benefit.

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

Chronic Phase CML - Newly Diagnosed Adults

An international open-label, multi-centre, randomised, comparative Phase III 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 end-point 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.

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 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, 61% of patients randomised to the SPRYCEL group and 63% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation due to disease progression occurred in 7% of SPRYCEL-treated patients and 9% of imatinib-treated patients.

Efficacy results are presented in Table 8. 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 8 Efficacy Results in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

	SPRYCEL n= 259	**imatinib n= 260**	**p-value[d]**
	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)	—
Cytogenetic Response within 24 months			
cCCyR[a]	80.3%	74.2%	—
CCyR[b]	87.3%	82.3%	—
Cytogenetic Response within 36 months			

cCCyR[a]	82.6%	77.3%	—
CCyR[b]	88.0%	83.5%	—
Cytogenetic Response within 48 months			
cCCyR[a]	82.6%	78.5%	-
CCyR[b]	87.6%	83.8%	-
Cytogenetic Response 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[e]
	Hazard Ratio		
	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[e]
Time-to MMR	1.54 (1.25-1.89)		p <0.0001[e]
Durability (Time-in) cCCyR	0.79 (0.55-1.13		p = 0.1983[e]

[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. The CCyR results refer to best unconfirmed cytogenic response within 12 months for any number of metaphases.
[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.
[d] Formal statistical comparison of cCCyR and MMR rates was only performed at the time of the primary endpoint (cCCyR within 12 months)
[e] P-values of secondary endpoints are nominal, that is, for descriptive purposes, and therefore not statistically significant*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.
**Not significant.
CI = confidence interval

For time-to cCCyR, a hazard ratio of 1.55 indicates that a patient treated with SPRYCEL is 55% more likely to achieve a cCCyR at any time compared to a patient treated with imatinib. Similarly, for time-to MMR, a hazard ratio of 2.01 indicates a patient treated with SPRYCEL is more than two times more likely to achieve a MMR at any time compared to a patient treated with imatinib. For durability of cCCyR (time-in response), a hazard ratio of 0.7 indicates a patient treated with SPRYCEL is 30% less likely to have disease progression after achieving a cCCyR (or never achieving a cCCyR) compared to a patient treated with imatinib.

After 60 months follow-up, median time to cCCyR was 3.1 months in the 214 SPRYCEL group responders and 5.8 months in the 204 imatinib group responders. Median time to MMR after 60 months follow-up was 9.3 months in the 196 SPRYCEL group responders and 15.0 months in the 163 imatinib group responders. 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. With a minimum of 60 months follow up, the rate of CMR (i.e. at least 4.5-log reduction from a standardised baseline value BCR-ABL ratio ≤ 0.0032%) at any time was 44% versus 34% in the SPRYCEL and imatinib treatment groups, respectively.

In an exploratory subgroup analysis 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 exploratory analysis, more SPRYCEL-treated subjects (84%) achieved early molecular response (defined as BCR-ABL levels ≤10% at 3 months) compared with imatinib-treated subjects (64%). Subjects 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 9 and Table 10.

Table 9 SPRYCEL-treated Subjects with BCR-ABL ≤10% and >10% at 3 Months

Dasatinib N = 235	**Subjects with BCR-ABL ≤10% at 3 Months**	**Subjects with BCR-ABL >10% at 3 Months**
Number of Subjects (%)	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)

Table 10 Imatinib-treated Subjects with BCR-ABL ≤10% and >10% at 3 Months

Imatinib (n = 239)	Subjects with BCR-ABL ≤10% at 3 Months	Subjects with BCR-ABL >10% at 3 Months
Number of Subjects (%)	154 (64.4)	85 (35.6)
Transformation at 60-months, n/N (%)	5/154 (3.2)	13/85 (15.3)
Rate of PFS at 60 Months (95% CI)	93.5% (87.8, 96.6)	79.3% (67.3, 87.3)
Rate of OS at 60 Months (95% CI)	95.4% (90.5, 97.8)	80.5% (70.1, 87.6)

The progression-free survival rate by specific timepoint is displayed graphically in Figure 1. Rate of PFS was consistently higher in SPRYCEL-treated patients who achieved BCR-ABL level ≤10 percent at 3 months than those who did not.

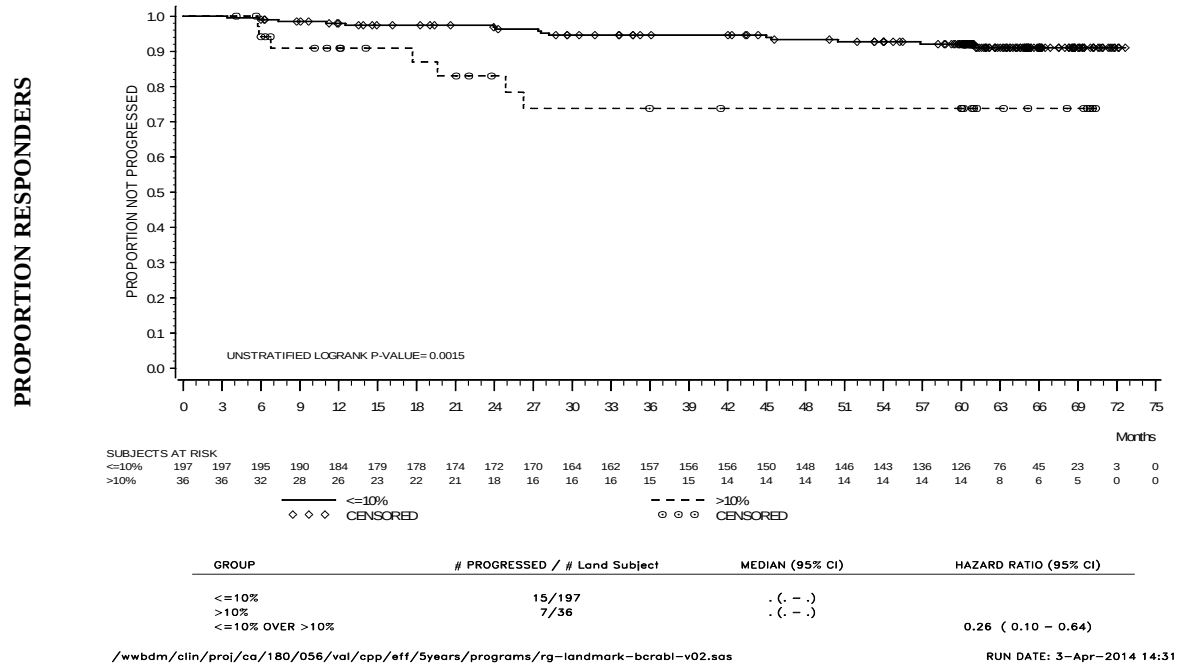


Figure 1 Landmark Plot for Progression-free Survival for SPRYCEL by BCR ABL Level (≤10% or >10%) at 3 Months in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

The overall survival rate by specific timepoint is displayed graphically in Figure 2. Rate of OS was consistently higher in SPRYCEL-treated patients who achieved BCR-ABL level ≤10 percent at 3 months than those who did not.

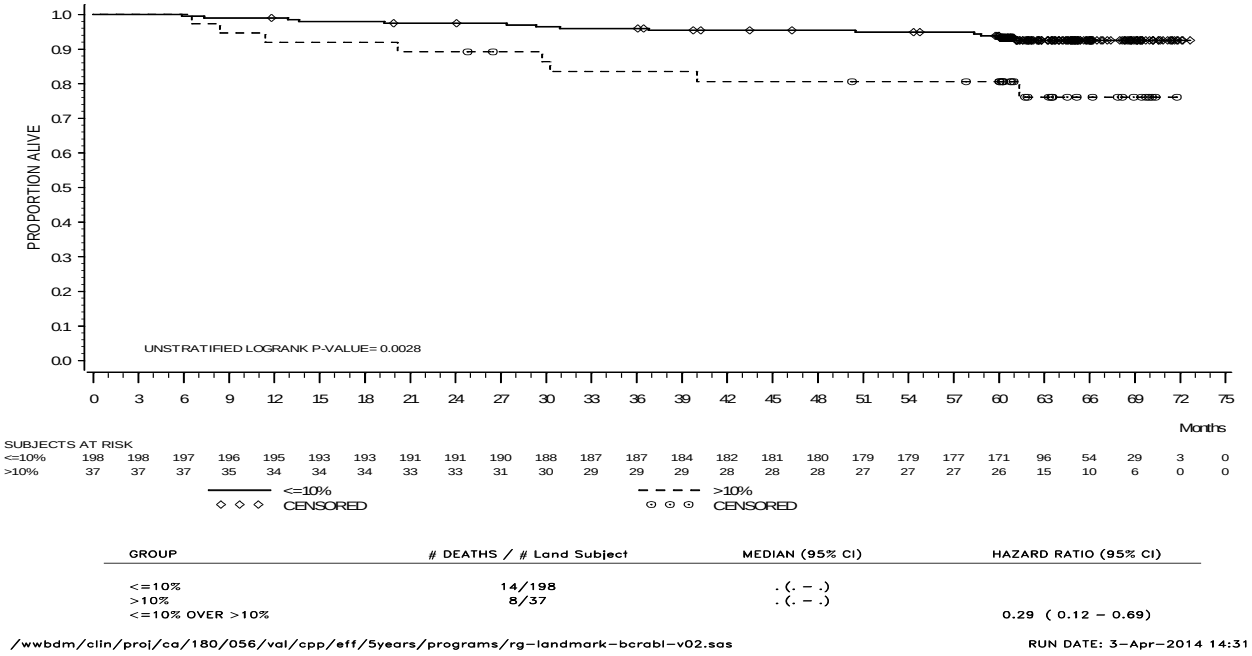
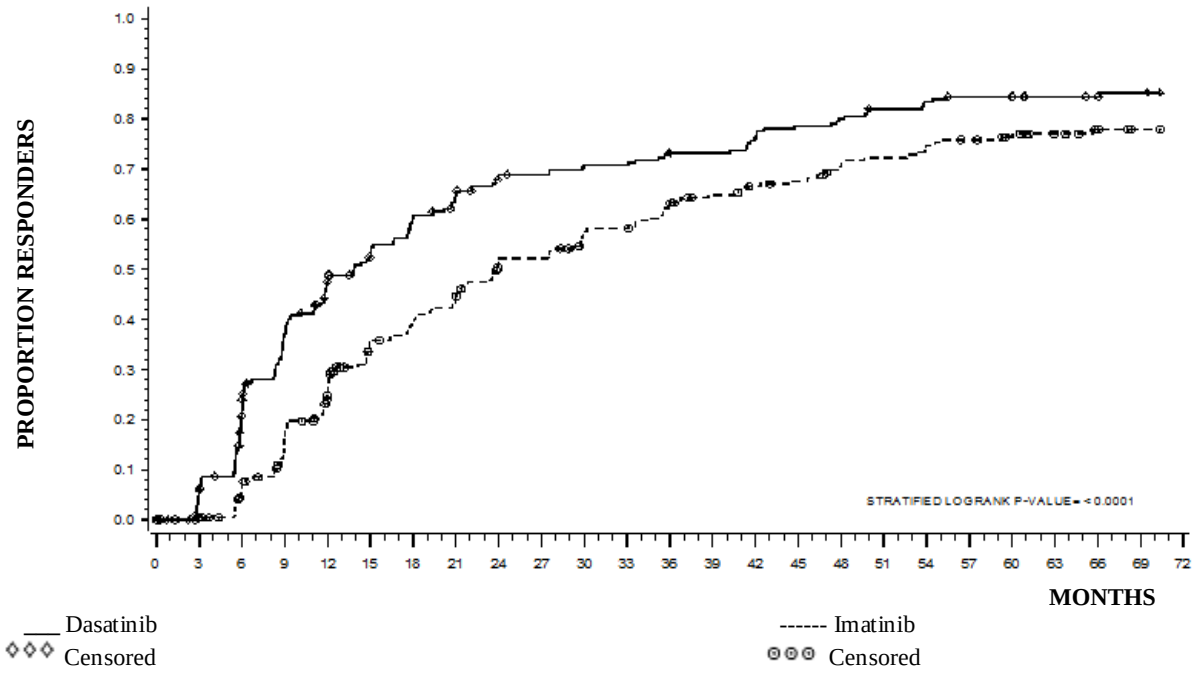


Figure 2 Landmark Plot for Overall Survival for TRADEMARK by BCR-ABL Level (≤10% or >10%) at 3 Months in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

The time to MMR is displayed graphically in Figure 3. The time to MMR was consistently shorter in SPRYCEL-treated subjects compared with imatinib-treated subjects.



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

Figure 3 Kaplan-Meier Estimate of Time to Major Molecular Response (MMR) in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

MMR rates by specific timepoint are displayed graphically in Figure 4. Rates of MMR were consistently higher in SPRYCEL-treated subjects compared with imatinib-treated subjects.

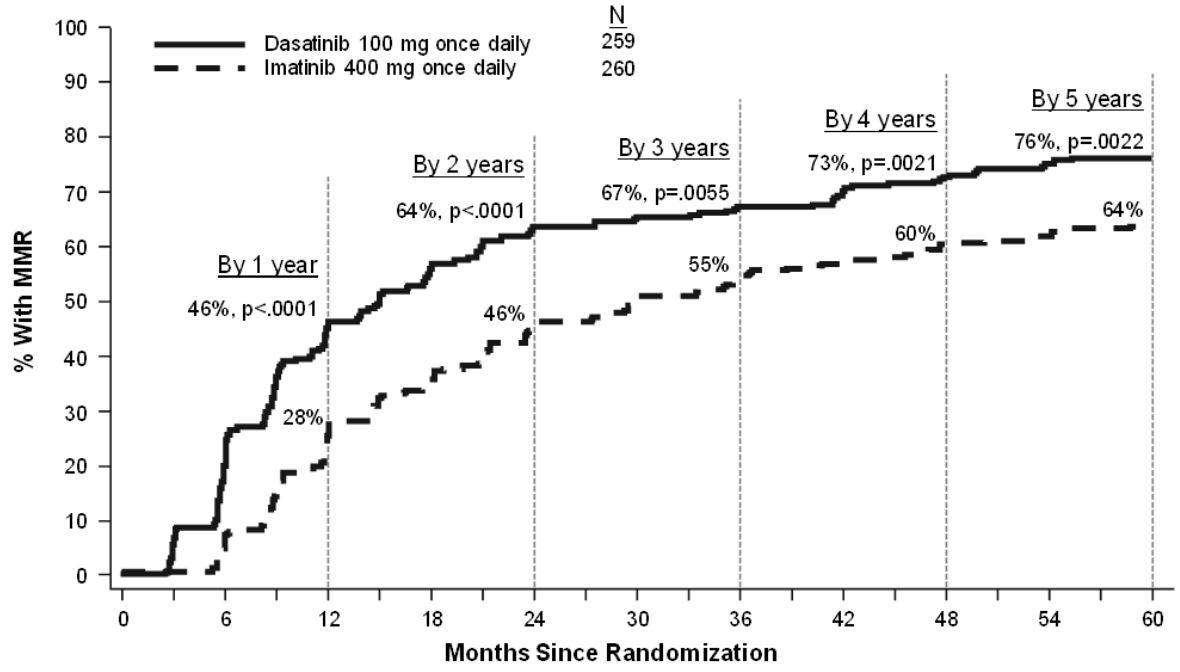


Figure 4 MMR Rates Over Time - All Randomized Subjects in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

MR4.5 rates over time are displayed graphically in Figure 5. Rate of MR4.5 over time was consistently higher in SPRYCEL-treated subjects compared with imatinib-treated subjects.

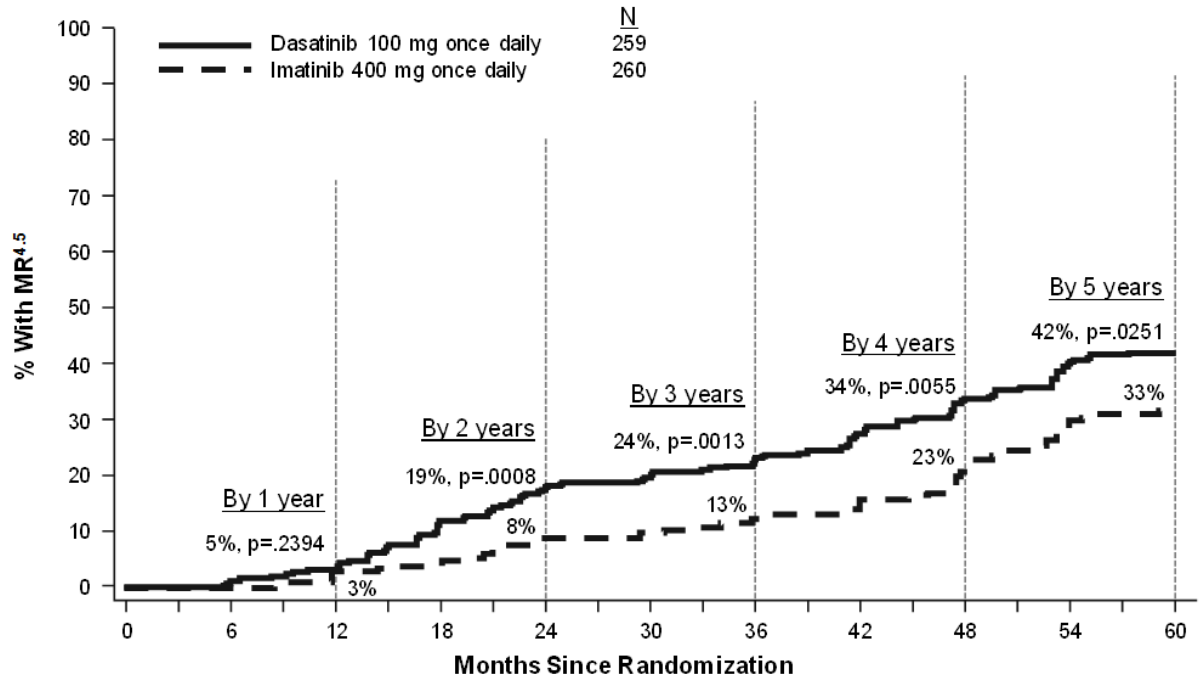


Figure 5 MR4.5 Rates Over Time - All Randomized Subjects in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

Disease progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR (complete haematologic response), partial CyR or CCyR, progression to accelerated phase or blast phase, or death. The estimated 60-month PFS rate was 88.9% (CI: 84.0% - 92.4%) and 89.2% (CI: 84.3% - 92.7%) for the SPRYCEL and imatinib treatment groups, respectively. Transformation to accelerated or blast phase occurred less frequently with SPRYCEL (n = 8; 3.1%) than with imatinib-treated patients (n = 15; 5.8%). The estimated 60-month survival rates for SPRYCEL and imatinib-treated patients were 90.9% (CI: 86.6% - 93.8%) and 89.6% (CI: 85.2% - 92.8%) respectively.

In a phase III trial of newly diagnosed chronic phase CML, BCR-ABL sequencing was performed on blood samples from patients who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L and V299L. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data.

Phase III Clinical Trials 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 SPRYCEL administered once daily compared with SPRYCEL administered twice daily: The results described in Tables 11 and 12 are based on a minimum of 24 months and 60 months follow-up after the start of dasatinib therapy.

In the non- inferiority study in chronic phase CML, the primary endpoint was MCyR (once daily vs. twice daily) 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, progression-free survival, and overall survival. A total of 670 patients, of whom 497 were imatinib-resistant, were randomised to the SPRYCEL 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. The non-inferiority criteria were met for the primary efficacy endpoint at 6 months analysis. Results for each of the 4 individual regimens demonstrated comparable efficacy for MCyR and for a variety of secondary endpoints. At 2-Year analysis, the median duration of treatment

was approximately 22 months (range <1 to 31 months). In patients with resistant or intolerant chronic phase CML, the median duration of treatment for patients still on therapy (n=205) was 59 months (range 28 to 66 months).

Efficacy results at 2 year analysis are presented in Tables 11 and 12. 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 end-point (difference in MCyR 1.9%; 95% confidence interval [-6.8% - 10.6%]). However, the 100 mg once daily regimen had improved tolerability.

Table 11 Efficacy of SPRYCEL in Phase III Dose-Optimisation Study: Chronic Phase CML (2 year results)[a]

All Patients	**n = 167**
Imatinib-Resistant Patients	**n = 124**
Haematologic 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 [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] **Haematologic response criteria** (all responses confirmed after 4 weeks):
Complete haematologic response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets < 450 x 10^9/L, 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.
Molecular response was evaluated in a subset of assessed patients who had a CCyR
CI = confidence interval; ULN = upper limit of normal range.

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% with a minimum of 2 years follow-up.

Approximately 20% of subjects remained on study therapy through study completion (i.e. a minimum of 7 years), discontinuing study treatment due to study closure. Table 12 represents the comparative data (1 – 7 years), for the recommended starting dose 100 mg once daily in CML chronic phase.

Table 12 Long Term Efficacy of SPRYCEL in Phase III Dose Optimization study: Imatinib Resistant or Intolerant Chronic Phase CML[a]

	Minimum Follow-up Period			
	1 year	**2 years**	**5 years**	**7 years**
Major Molecular Response				
All subjects	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 subjects	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 subjects	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.

In the Phase III, randomized, open-label study in patients with advanced phase CML and Ph+ALL, whose disease was resistant to or who were intolerant to imatinib, the primary endpoint was MaHR. A total of 611 patients were randomised to either the SPRYCEL 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range <1-31 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%]); The response rates are presented in Table 13.

Table 13 Efficacy of SPRYCEL in Phase III Dose-Optimisation Study: Advanced Phase CML and Ph+ ALL (2 year results)[a]

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

[a] Results reported in recommended starting dose of 140 mg once daily.

[b] Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response (MaHR) = complete haematologic response (CHR) + no evidence of leukaemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥ 1.0 x 10^9/L, platelets ≥ 100 x 10^9/L, 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 ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L , or platelets ≥ 20 x 10^9/L and ≤ 100 x 10^9/L.

[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 once daily regimen, the median duration of MaHR and the median overall survival in patients with accelerated phase CML was not reachedfor either group; the median PFS was 25 months and 26 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; and the median overall survival was not reached for the 140 mg once daily group and 31 months for the 70 mg twice daily group.

In patients with myeloid blast phase CML treated with the 140 mg once daily regimen the median duration of MaHR was 8 months, and 9 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months for both groups; and the median overall survival was 8 months for both groups. In patients with lymphoid blast phase CML, the median duration of MaHR was 5 months and 8 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 5 months for both groups, and the median overall survival was 11 months and 9 months, respectively.

In patients with Ph+ALL treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months and 12 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months and 3 months respectively, and the median overall survival was 7 months and 9 months, respectively.

Ph+ ALL - Newly Diagnosed Adults

A total of 426 newly diagnosed adult Ph+ ALL patients have been treated with dasatinib integrated with chemotherapy in 11 phase II clinical trials. The efficacy results from 4 pivotal phase II studies are summarised below.

In a phase II study, Ravandi et al reported on seventy-two (72) newly diagnosed Ph+ ALL patients (median age 55, range 21 – 80 years) treated with dasatinib (100 mg once a day or 50 mg twice a day on days 1-14 of each chemotherapy cycle) integrated with a HyperCVAD chemotherapy protocol during induction, followed by dasatinib 100 mg once a day or 50 mg twice a day as maintenance. Sixty

nine (96%) achieved CR. Among them, 57 (83%) achieved cytogenetic CR after 1 cycle, and 64 (93%) achieved a major molecular response at a median of 4 weeks (range, 2-38 weeks). Sixty-five patients (94%) were negative for minimal residual disease assessed by flow cytometry at a median of 3 weeks (range, 2-37 weeks). With a median follow-up of 67 months (range, 33-97 months), 33 patients (46%) were alive, and 30 (43%) were in CR. The 5 year disease free survival (DFS) and overall survival (OS) outcomes estimated via Kaplan-Meier method were 44% and 46% respectively.

Yoon et al reported on a phase II clinical study in 51 newly diagnosed Ph+ ALL patients (median age 46 range 19-64 years) treated with 2 cycles of dasatinib (100 mg once daily) integrated with chemotherapy (each cycle included 4 weeks) during induction and upto 4 cycles as consolidation followed by 2 years of maintenance with dasatinib. After the first dasatinib cycle, 50 patients (98.0%) achieved CR. By the end of the second dasatinib cycle, 46 (93.9%) of 49 assessable patients had persistent CR with 39 progressing to allogenic stem cell transplant. After a median follow-up of 54 months (range 40-63), the 4-year cumulative incidence of DFS and OS rate for all patients were 52.0% and 51%, respectively.

Rousellot et al investigated dasatinib, in combination with low-intensity chemotherapy in 71 newly diagnosed patients with Ph+ All, over 55 years of age (median 69, range 59 – 83). Patients were treated with dasatinib 140 mg/day (100 mg/day over 70 years) plus intrathecal chemotherapy, vincristine, and dexamethasone during induction. Patients in complete remission continued consolidation with dasatinib, sequentially with cytarabine, asparaginase, and methotrexate for 6 months. Maintenance therapy was dasatinib and vincristine/dexamethasone reinductions for 18months followed by dasatinib until relapse or death. 96% of patients achieved CR at induction and 7 patients underwent allogenic stem cell transplant. After a median follow up of 66 months (21 – 88) 5year Event Free Survival (EFS), and OS were 27% (95%CI, 17-37), and 36% (95%CI, 25-47) respectively.

In the GIMEMA LAL1205 study published by Foá et al, 53 patients with newly diagnosed Ph+ ALL older than 18 years (median age 54, range 23-76 years) received dasatinib (70 mg twice daily) induction therapy for 84 days combined with steroids for the first 32 days and intrathecal chemotherapy. Post remission therapy was not specified. All patients achieved a complete hematologic remission (CHR). At 20 months, the overall survival was 69.2% and disease-free survival was 51.1%.

Chronic Phase CML – paediatric patients

The efficacy of SPRYCEL in paediatric patients was evaluated in two paediatric studies in which 97 patients with chronic phase CML received SPRYCEL tablets. Among 97 patients with chronic phase CML treated in two paediatric 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; 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 paediatric 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 paediatric studies are summarized in Table 14.

Table 14 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 14 Efficacy of SPRYCEL in Paediatric Patients with CP-CML Cumulative Response Over Time by Minimum Follow-Up Period

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

[a] Patients from paediatric study of newly diagnosed CP-CML receiving oral tablet formulation
[b] Patients from paediatric studies of imatinib-resistant or -intolerant CP-CML receiving oral tablet formulation

With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, MMR could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.5+ to 66.5+ months for CCyR), (1.4 to 66.5+ months for MCyR), and (5.4+ to 72.5+ months for subjects who achieved MMR by month 24 and 0.03+ 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-naïve 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-naïve 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 – paediatric patients

The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort of Study CA180372 (NCT01460160), a multicenter study of paediatric 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%.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of SPRYCEL were evaluated in 235 healthy subjects and in 84 patients with leukaemia.

Absorption

Dasatinib is rapidly absorbed in patients following oral administration. The absolute bioavailability of dasatinib has not been determined. Peak concentrations were observed between 0.5 and 6 hours. Following oral administration, the increase in the mean exposure (AUC_τ) is approximately proportional to the dose increment across doses ranging from 15 mg to 240 mg daily.

Data from a study of healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects are unlikely to be clinically significant. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44% CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30% and 32% CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy.

Distribution

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

Metabolism

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

Excretion

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

Special Populations

Age and gender

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

Hepatic impairment

The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic-impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of dasatinib. The mean C_{max} and AUC of dasatinib adjusted for the 70 mg dose was decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean C_{max} and AUC adjusted for the 70 mg dose was decreased by 43% and 28% respectively, compared to subjects with normal hepatic function (see Section 4.4 Special warnings and precautions – Use in hepatic impairment and Section 4.2 Dose and method of administration – Special populations).

Paediatric patients

The pharmacokinetics of dasatinib film-coated tablets was evaluated in 72 paediatric patients with relapsed or refractory leukaemia or solid tumors at oral doses ranging from 60 to 120 mg/m2 once daily and 50 to 110 mg/m2 twice daily. Data was pooled across two studies and showed that the tablet was rapidly absorbed. Mean Tmax was observed between 0.5 and 6 hours and mean half-life ranged from 2 to 5 hours across all dose levels and age groups. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in paediatric patients. There was no significant difference of dasatinib PK between children and adolescents. The geometric means of dose-normalized dasatinib C_{max}, AUC (0-T), and AUC (INF) appeared to be similar between children and adolescents at different dose levels. A population pharmacokinetic (PPK) model-based simulation predicted that the body weight tiered dosing recommendation described for SPRYCEL tablets (see 4.2 Dose and method of

administration – Paediatric dosage) is expected to provide similar exposure to a tablet dose of 60 mg/m^2. The bioavailability of dispersed tablets in paediatric patients was estimated to be 36% lower than that of intact tablets.

Renal impairment

There are no clinical studies of SPRYCEL in patients with impaired renal function. Less than 4% of dasatinib and its metabolites are excreted via the kidney (see Section 4.4 Special warnings and precautions – Use in renal impairment and Section 4.2 Dose and method of administration – Special populations).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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 or slightly lower than calculated human exposure at the recommended range of starting doses 100 mg or 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 female rats and of prostate adenoma in low-dose male rats was noted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hyprolose
Magnesium stearate

Film- coating

Hypromellose
Titanium dioxide
Polyethylene glycol

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

SPRYCEL tablets should be stored below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

SPRYCEL 20 mg, 50 mg and 70 mg tablets are available in high density polyethylene (HDPE) bottles with child-resistant closure or blisters of 60 tablets. SPRYCEL 100 mg tablets are available in HDPE bottles with child-resistant closure or blisters of 30 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

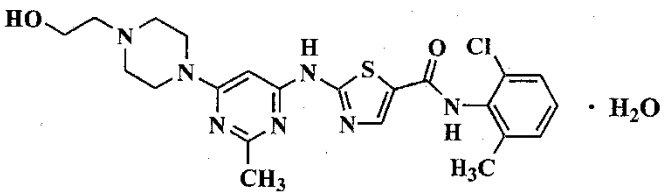
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

SPRYCEL 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 and/or broken tablets.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Dasatinib drug substance has the following chemical structure:



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 $C_{22}H_{26}C1N_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01.

The drug substance is insoluble in water (0.008 mg/mL) at 24 ± 4 ºC. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pK_a) were determined to be 6.8 and 3.1, and one weakly acidic pK_a was determined to be 10.8. The solubilities of dasatinib in various solvents at 24 ± 4 ºC are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil.

CAS number

The CAS number for dasatinib monohydrate is 863127-77-9.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

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Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

20 mg, 50 mg, 70 mg: 15 January 2007

100 mg: 16 February 2010

10 DATE OF REVISION OF THE TEXT

26 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of Hepatotoxicity
4.8	Addition of Hepatotoxicity in Post Marketing Experience
5.2	Formatting update
6.5	Editorial update

SPRYCEL® is a registered trademark of Bristol-Myers Squibb Company.