DATA SHEET

1 PRODUCT NAME

SPRYCEL® 20 mg film-coated tablets

SPRYCEL® 50 mg film-coated tablets

SPRYCEL® 70 mg film-coated tablets

SPRYCEL® 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SPRYCEL 20 mg film-coated tablets
Each film-coated tablet contains 20 mg dasatinib (as monohydrate).
Excipient with known effect
Each film-coated tablet contains 27 mg of lactose monohydrate.

SPRYCEL 50 mg film-coated tablets
Each film-coated tablet contains 50 mg dasatinib (as monohydrate).
Excipient with known effect
Each film-coated tablet contains 67.5 mg of lactose monohydrate.

SPRYCEL 70 mg film-coated tablets
Each film-coated tablet contains 70 mg dasatinib (as monohydrate).
Excipient with known effect
Each film-coated tablet contains 94.5 mg of lactose monohydrate.

SPRYCEL 100 mg film-coated tablets
Each film-coated tablet contains 100 mg dasatinib (as monohydrate).
Excipient with known effect
Each film-coated tablet contains 135.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SPRYCEL 20 mg film-coated tablets
White to off-white, biconvex, round film-coated tablet with "BMS" debossed on one side and "527" on the other side.

SPRYCEL 50 mg film-coated tablets
White to off-white, oval shaped film-coated tablet with "BMS" debossed on one side and "528" on the other side.

SPRYCEL 70 mg film-coated tablets
White to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side.

SPRYCEL 100 mg film-coated tablets
White to off-white, oval shaped film-coated tablet with "BMS 100" debossed 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 chronic myeloid leukaemia (CML).
- chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.
- 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

Adult Dosage

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

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.

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 Interaction with other medicines and other forms of interaction**).

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

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 (newly diagnosed patients) (starting dose 100 mg once daily)	ANC* <0.5 × 10^9/L or Platelets <50 × 10^9/L	1. Stop SPRYCEL until ANC ≥1.0 × 10^9/L and platelets ≥50 × 10^9/L. 2. Resume treatment with SPRYCEL at the original starting dose. 3. If platelets <25 × 10^9/L or recurrence of ANC <0.5 × 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 × 10^9/L or Platelets <10 × 10^9/L	1. Check if cytopaenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1.0 × 10^9/L and platelets ≥20 × 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 cytopaenia is related to leukaemia, 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 cytopaenia is related to leukaemia (marrow aspirate or biopsy).	40 mg	20 mg	**
2. If cytopaenia is unrelated to leukemia, stop SPRYCEL until ANC* ≥1.0 × 10^9/L and platelets ≥75 × 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 cytopaenia 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 109/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-Haematological 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-haematological 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 80 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 **4.4 Special warnings and precautions for use**).

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 **4.4 Special warnings and precautions for use**).

Renal impairment: Since the renal clearance of dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency (see **4.4 Special warnings and precautions for use**).

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

General

Myelosuppression

Treatment with SPRYCEL is associated with thrombocytopenia, neutropenia and anaemia which occur earlier and more frequently in patients with advanced 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 **4.2 Dose and method of administration** and **4.8 Undesirable effects: Laboratory Abnormalities**). CTC Grade 3 or 4 (severe) cases of anaemia were managed with blood transfusions.

Bleeding Related Events

In the Phase III study in patients with chronic phase CML, 5 patients (1%) receiving SPRYCEL at the recommended dose (n=548) had Grade 3 or 4 haemorrhage. In clinical studies in patients with advanced phase CML or Ph+ ALL, severe (Grade 3 to 5) CNS haemorrhage, including fatalities, occurred in 1% of patients receiving SPRYCEL at the recommended dose (n=304)**.** Eight cases were fatal and 6 of them were associated with Common Toxicity Criteria (CTC) Grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage, including fatalities, occurred in 6% of patients and generally required treatment interruptions and transfusions. Other cases of Grade 3 or 4 haemorrhage occurred in 2% of patients. 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), Grade 3 or 4 fluid retention was reported in 13 patients (5%) receiving dasatinib compared to 2 patients (1%) receiving imatinib (n=258) (see **4.8 Undesirable effects**). In all patients with newly diagnosed or imatinib resistant or intolerant patients with chronic phase CML (n-548), severe fluid retention occurred in 32 (6%) patients receiving SPRYCEL at the recommended dose. In patients with advanced phase CML or Ph+ ALL receiving SPRYCEL at the approved dose (n=304), Grade 3 or 4 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% 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 steroid. Severe pleural effusion may require oxygen therapy and thoracentesis. Dose modification should be considered.

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 phase II, single-arm clinical studies in 865 patients with leukaemia treated with SPRYCEL 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.

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 dyspnea and fatigue after initiation of therapy should be evaluated for more common etiologies including pleural effusion, pulmonary edema, anemia, or lung infiltration. During this evaluation, guidelines for non-hematologic adverse reactions should be followed (see **4.2 Dose and method of administration**): if the adverse reaction is severe, treatment must be withheld until the event has resolved or improved. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, SPRYCEL 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.

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.

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. Adverse cardiac events were more frequent in patients with risk factors or a previous medical historyof cardiac disease. Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see **4.8 Undesirable effects**).

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

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 tablets contain 135 mg lactose in a 100 mg daily dose and 189 mg of lactose 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.

Hepatic Impairment

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

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 concentration >3 times the upper limit of normal range, and clinical studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range). Dasatinib and its metabolites are minimally excreted via the kidney. Since the renal excretion of unchanged dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

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.

Geriatric Use

No differences in cCCyR and MMR were observed between older and younger patients. Of the 2712 patients in clinical studies of SPRYCEL, 617 (23%) were 65 years of age and older and 123 (5%) were 75 years of age and older. While the safety profile of SPRYCEL in the geriatric population is similar to that in the younger population, 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%), lower gastrointestinal haemorrhage (2.4% vs 0.7%), 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%), 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. No differences in efficacy were observed

between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and older.

4.5 Interaction with other medicines and other forms of interaction

Medicines 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, indinavir, nelfinavir, sequinavir, telithromycin, 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.

Medicines that may decrease dasatinib plasma concentrations

CYP3A4 Inducers: Medicines that induce CYP3A4 activity may increase metabolism and decrease dasatinib plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) with SPRYCEL 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: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with SPRYCEL reduced the AUC of a single dose of SPRYCEL by 55% and the Cmax 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. In a study of 14 healthy subjects, administration of a single 100 mg dose of SPRYCEL 22 hours following a 4 day, 40 mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C_{max} of dasatinib by 42%. The concomitant use of 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 (at least 2 hours prior to or 2 hours after the dose of SPRYCEL should be considered in place of histamine-2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

Medicines that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: Dasatinib is an inhibitor of CYP3A4. In a study in healthy subjects, a single 100mg dose of SPRYCEL increased exposure to simvastatin, a known CYP3A4 substrate, by 20%. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporin, fentanyl, pimozide, quinidine, sirolimus, tacrolimus,

bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL (See **5. PHARMACOLOGICAL PROPERTIES**).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category D

Dasatinib can cause foetal harm when administered to a pregnant woman. There have been post-marketing reports of spontaneous abortion and foetal and infant anomalies from women who have taken SPRYCEL during pregnancy. In nonclinical studies, at exposure levels that are readily achievable in humans receiving therapeutic doses of SPRYCEL serious embryo foetal toxicity was observed in both pregnant rats and rabbits. Malformations (including skeletal alterations) and foetal death were observed in rats treated with dasatinib. (See **5.3 Preclinical safety data: Carcinogenesis, Mutagenesis, Impairment of Fertility**.)

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 foetus.

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 **5.3 Preclinical safety data: Carcinogenesis, Mutagenesis, Impairment of Fertility**). However, data evaluating reproductive toxicity in male patients taking SPRYCEL is limited.

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

Use in Lactation

It is unknown whether SPRYCEL is excreted in human milk. Women who are taking SPRYCEL should not breastfeed.

4.7 Effects on ability to drive and use machines

SPRYCEL has minor influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with dasatinib. Therefore, caution should be recommended when driving a car or operating machines

4.8 Undesirable effects

SPRYCEL as a 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 , 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 SPRYCEL-treated patients experienced adverse reactions at some time, regardless of dose or schedule. In the overall population of 2712 SPRYCEL-treated adult subjects, 520 (19%) experience adverse 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 97 paediatric patients with chronic phase CML, 1 (1%) experienced adverse reactions leading to treatment discontinuation.

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-glutamyltransferase increase

Cardiac disorders

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

Uncommon: electrocardiogram QT prolonged, myocardial infarction (including fatal outcomes), 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, VIIth 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: vertigo, hearing loss

Respiratory, thoracic and mediastinal disorders

Very Common: pleural effusion, dyspnea

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

Uncommon: bronchospasm, asthma, dysphonia, pulmonary arterial hypertension

Rare: acute respiratory distress syndrome, pulmonary embolism

Gastrointestinal disorders

Very Common: diarrhoea, nausea, vomiting, abdominal pain

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

Uncommon: pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, 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: pruritis, alopecia, dermatitis (including eczema), 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: muscular weakness, arthralgia, myalgia, 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], hyperuricemia

Uncommon: hypoalbuminaemia, dehydration, 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 outcomes)

Injury, poisoning, and procedural complications

Common: contusion

Vascular disorders

Very Common: haemorrhage[d]

Common: hypertension, flushing

Uncommon: hypotension, thrombophlebitis

Rare: livedo reticularis, deep vein thrombosis, embolism

General disorders and administration site conditions

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

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

Uncommon: malaise, temperature intolerance, 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, peurperium 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 5 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

Postmarketing Experience

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

Laboratory Abnormalities

Haematology and Biochemistry in patients with newly diagnosed chronic phase CML

The comparative frequency of Grade 3 and 4 laboratory abnormalities in patients with newly diagnosed chronic phase CML is presented in Table 6. There were no discontinuations of SPRYCEL therapy due to the biochemical laboratory parameters.

Table 6: CTC Grade 3/4 Laboratory Abnormalities in a Phase III Study of Patients with Newly Diagnosed Chronic Phase CML

	SPRYCEL n= 258	**imatinib n= 258**
	Percent (%) of Patients	
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 8 shows laboratory findings from clinical trials in adult CML patients with imatinib resistance or intolerance received at 24 months of follow up.

Table 8: CTC Grades 3/4 Laboratory Abnormalities in Studies of in Patients with CML Resistant or Intolerant to Prior Imatinib Therapy

	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=135)
	Percent (%) of Patients				
Haematology Parameters*					
Neutropenia	35	58	77	79	75
Thrombocytopenia	23	63	78	85	71
Anemia	13	47	74	52	42
Biochemistry Parameters					
Hypophosphatemia	10	13	12	18	21
Hypokalemia	2	7	11	15	16
Hypocalcemia	<1	4	9	12	9
Elevated SGPT (ALT)	0	2	5	3	7
Elevated SGOT (AST)	<1	0	4	3	4
Elevated Bilirubin	<1	1	3	6	2
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 dailyCTC 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 <7.0–6.0mg/dL, Grade 4 <6.0mg/dL); hypophosphataemia (Grade 3 <2.0–1.0mg/dL, Grade 4 <1.0mg/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 of transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdosage of 280mg per day for one week was reported in 2 patients and both developed a significant decrease in platelet count. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE06.

Mechanism of Action

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

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

In a phase III trial of adult patients with 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.

Clinical Efficacy and Safety

Paediatric patients

Chronic Phase CML

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/m2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Baseline demographic characteristics of the 46 imatinib resistant or intolerant patients were: median age 13.5 years (range 2 to 20 years), 78.3% White, 15.2% Asian, 4.4% Black, 2.2% other, and 52%

female. Baseline characteristics of the 51 newly diagnosed patients were: median age 12.8 years (range 1.9 to 17.8 years), 60.8% White, 31.4% Asian, 5.9% Black, 2% Other, and 49% female.

Median duration of follow-up was 5.2 years (range 0.5 to 9.3 years) for the imatinib resistant or intolerant patients and 4.5 years (range 1.3 to 6.4 years) for the newly diagnosed patients, respectively. Efficacy results for the two 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 6 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
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/m2 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 (dasatinib) 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, 100mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects are unlikely to be clinically significant. 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 medicine is extensively distributed in the extravascular space.

Metabolism

Dasatinib is extensively metabolized in humans. In a study of 8 healthy subjects administered 100mg 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 medicine. The overall mean terminal half-life of dasatinib is approximately 5-6 hours. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Elimination

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [^{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**.**

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 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use).

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/m^2 once daily and 50 to 110 mg/m^2 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 Cmax, 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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 medicine exposure (AUC) level generally equivalent to the human exposure at the recommended range of starting doses from 100 mg to 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose female rats and of prostate adenoma in low-dose male rats was noted. The relevance of the findings from the rat carcinogenicity study for humans is not known.

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.

Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryolethality at dose levels approximating human clinical exposures. In embryofetal development studies, dasatinib likewise induced embryolethality with associated decreases in litter size in rats as well as fetal skeletal alterations, including malformations, in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis. In an exploratory peri- and post-natal development study, indirect exposure of rat pups to dasatinib (*in utero* or through lactation) initiating from the end of organogenesis through early lactation was incompatible with pup survival, even at maternal exposures that are subtherapeutic.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropylcellulose
Magnesium stearate

Film-coating
Hypromellose
Titanium dioxide
Macrogol 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months. Stored at or below 30°C.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
SPRYCEL 20 mg, 50 mg and 70 mg film-coated tablets
Blister pack, Al/Al. 60 tablets
Bottle, plastic, HDPE. 60 tablets

SPRYCEL 100 mg film-coated tablets
Blister pack, polyamide film/aluminium foil/PVC base with primer and heat seal coated aluminium lidding foil. 30 tablets
Bottle, plastic, 95 mL HDPE bottle with PP cap and silica gel desiccant. 30 tablets

6.6 Special precautions for disposal

Preparation and Administration Precautions

Procedures for proper handling and disposal of anticancer medicines 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 (dasatinib) tablets consist of a core tablet (containing the active medicine substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active medicine substance. The use of gloves when handling the tablets is recommended, especially if the tablets are crushed or broken. Health care professionals should wear disposable chemotherapy gloves for appropriate disposal in order to minimise the risk of dermal exposure. Any unused product or waste material should be disposed of in accordance with local requirements. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

Bristol-Myers Squibb (NZ) Limited
Auckland, New Zealand

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9 DATE OF FIRST APPROVAL

SPRYCEL 20 mg, 50 mg and 70 mg film-coated tablets: 7 May 2009

SPRYCEL 100 mg film-coated tablets: 16 December 2009

10 DATE OF REVISION OF THE TEXT

24 November 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

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