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

4.2 Dose and method of administration

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

In clinical studies, treatment with SPRYCEL 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.

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.

Dose Escalation

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

Dose Adjustment for Adverse Reactions

Myelosuppression

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

Table 1	**Dose Adjustments for Neutropenia and Thrombocytopenia**	
Chronic Phase CML (starting dose 100mg once daily)	ANC* <0.5 x 10^9/L and/or Platelets <50 x 10^9/L	1. Stop SPRYCEL until ANC ≥1.0 x10^9/L and platelets ≥50 x10^9 /L 2. Resume treatment with SPRYCEL at the original starting dose 3. If platelets <25 x10^9/L and/or recurrence of ANC <0.5 x 10^9 /L for >7 days, repeat step 1 and resume SPRYCEL at a reduced dose of 80mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* <0.5 x 10^9/L and/or Platelets <10 x 10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukaemia, stop SPRYCEL until ANC ≥1.0 x 10^9 /L and platelets ≥20 x 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 leukaemia, consider dose escalation to 180 mg once daily.
*ANC: absolute neutrophil count		

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 50 mg once daily, if needed, is recommended.

Paediatric population: The safety and efficacy of SPRYCEL in children and adolescents below 18 years of age have not yet been established. No data are available (see **4.4 Special warnings and precautions for use**).

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**).

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. 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**).

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 treated with dasatinib as monotherapy, complete blood counts (CBCs) should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated.

In adult 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.

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 or 4) 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.

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

Hepatic Impairment

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. Due to the limitations of this clinical study, caution is recommended when SPRYCEL 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 patients <18 years of age have not been established.

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.

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 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
The data described below reflect exposure to SPRYCEL at all dose studied in 324 patients with newly diagnosed chronic phase CML and in 2388 patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2712 SPRYCEL treated patients was 19.2 months (range 0-93.2 months).

In the Phase III study of patients with newly diagnosed chronic phase CML the median duration of therapy was approximately 60- months for both SPRYCEL (range 0.03-72.7 months) and imatinib (range 0.3-74.6 months). The median duration of therapy in 1618 patients with chronic phase CML was 29 months (range 0 to 92.9 months). In 1094 patients with advanced phase CML or Ph+ ALL, the median duration of treatment for patients was 6.2 months (range 0 to 93.2 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 subjects, 520 (19%) experience adverse reactions leading to treatment discontinuation.

In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for adverse reactions in 14% of SPRYCEL-treated patients and 7% of imatinib-treated patients with a minimum of 60 months follow-up. Among the 1618 SPRYCEL-treated subjects with chronic phase CML, adverse reactions leading to discontinuation were reported in 329 (20.3%) subjects, and among the 1094 SPRYCEL-treated subjects with advanced phase disease, adverse reactions leading to discontinuation were reported in 191 (17.5%) subjects.

The majority of imatinib-intolerant patients in chronic phase CML were able to tolerate treatment with SPRYCEL. In clinical studies with 24 months minimum follow-up in chronic phase CML, 10 of the 215 imatinib-intolerant patients had the same Grade 3 or 4 non-haematological toxicity with SPRYCEL, as they did with prior imatinib; 8 of the 10 patients were managed with dose reduction and were able to continue SPRYCEL treatment.

Adverse reactions reported in ≥10% of patients, and other adverse reactions of interest, in a Phase III trial of newly diagnosed chronic phase CML at a median follow-up of approximately 60 months are presented in Table 3. In this study, pleural effusion was reported in 73 patients (28%) receiving SPRYCEL. The median time to onset for Grade 1 or 2 pleural effusion events was 114 weeks (range 4-299 weeks). Fewer than 3% of pleural effusion events were Grade 3 or 4. With appropriate medical care, 58 patients (80% of those with pleural effusion) were able to continue on SPRYCEL (see **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**).

The most frequently reported adverse reactions in SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, skin rash, headache, haemorrhage, fatigue, nausea, dyspnoea, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. In the Phase III study in patients with resistance or intolerance to prior imatinib therapy, medicine-related febrile neutropenia was reported in 3.6% of SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy.

Based on 2 year pooled data, the use of SPRYCELis associated with fluid retention with Grade 3 and 4 cases in 11% of patients with resistance or intolerance to prior imatinib therapy. Grade 3 or 4 pleural

and pericardial effusion were reported in 7% and 2% of patients, respectively. Severe congestive heart failure/cardiac dysfunction was reported in 2% of patients. Grade 3 or 4 ascites and generalised oedema were each reported in < 1%. One percent of patients experienced severe pulmonary oedema. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

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

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

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

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see **4.4 Special warnings and precautions for use**).

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

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

Table 2: Adverse Reactions Reported in ≥ 10% of Patients in a Phase III Study (Newly Diagnosed Chronic Phase CML, minimum 60 month follow-up)

	All Grades		Grade 3/4	
	SPRYCEL n= 258	**imatinib n= 258**	**SPRYCEL n= 258**	**imatinib n= 258**
Preferred Term	**Percent (%) of Patients**			
Fluid Retention[e]	39	45	5	1
Superficial localised oedema	14	38	0	< 1
Pleural effusion	28	1	3	0
Generalised oedema	4	7	0	0
Pericardial effusion	4	1	1	0
Congestive heart failure/cardiac dysfunction[a]	2	1	< 1	< 1
Pulmonary hypertension	5	1	<1	0
Pulmonary oedema	1	0	0	0

Table 2: Adverse Reactions Reported in ≥ 10% of Patients in a Phase III Study (Newly Diagnosed Chronic Phase CML, minimum 60 month follow-up)

Diarrhoea	22	23	1	1
Nausea	10	25	0	0
Abdominal Pain	11	8	0	<1
Vomiting	5	12	0	0
Headache	13	11	0	0
Rash[b]	14	18	0	2
Fatigue	11	12	< 1	0
Musculoskeletal pain	14	17	0	< 1
Myalgia	7	12	0	0
Arthralgia	7	10	0	<1
Muscle spasm	5	21	0	< 1
Haemorrhage[c]	7	7	1	1
Gastrointestinal bleeding	2	1	1	0
Other bleeding[d]	6	6	0	1

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.

[c] Important adverse reaction of special interest with < 10% frequency.

[d] Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

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

A comparison of cumulative rates of selected adverse reactions in the Phase III study of newly diagnosed patients with chronic phase CML with minimum follow-up of one and five years are shown in Table 3.

Table 3: Selected Adverse Reactions Reported in a Phase III Study (Newly Diagnosed Chronic Phase CML (n=258))

	Minimum of 1 Year Follow Up		Minimum of 5 Years Follow Up	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	Percent (%) of Patients			
Fluid Retention[f]	19	1	39	5
Pleural effusion	8	0	28	3
Superficial localised oedema	9	0	14	0
Face oedema	6	0	10	0
Pulmonary hypertension	1	0	5	<1
Generalised oedema	2	0	4	0
Pericardial effusion	1	<1	4	1
Congestive heart failure/cardiac dysfunctiona	2	<1	2	1
Pulmonary oedema	<1	0	1	0
Diarrhoea	17	<1	22	1
Musculoskeletal pain	11	0	14	0
Rash[b]	11	0	14	0
Headache	12	0	13	0
Fatigue	8	<1	11	<1
Nausea	8	0	10	0
Myalgia	6	0	7	0
Arthralgia	5	0	7	0
Haemorrhage[c]	5	<1	7	1
Gastrointestinal bleeding	1	<1	2	1
Other bleedingd	4	0	6	0
Vomiting	5	0	5	0
Muscle spasm[e]	4	0	5	0

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.

[c] Adverse reaction of special interest with < 10% frequency.

[d] Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

[e] In the 60 month analysis the term “muscle inflammation” was re-mapped to “muscle spasm”

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

In the Phase III dose-optimisation study in patients with chronic phase CML resistant or intolerant to imatinib, the overall median duration of therapy was approximately 30 months (range <1 to 93 months), with a median duration in the 100 mg once daily group of 37 months (range 1 to 91 months). Cumulative rates of selected adverse reactions that were reported in the 100 mg once daily recommended starting dose are shown in Table 4.

Table 4: Phase III Dose-Optimisation Study: Chronic Phase CML (Imatinib Intolerant or Resistant Chronic Phase CML)[a]

	Minimum of 2 Years Follow Up		Minimum of 5 Years Follow Up		Minimum of 7 Years Follow Up	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	**Percent (%) of Patients**					
Diarrhoea	21	2	28	2	28	2
Fluid Retention[b]	34	4	42	6	48	7
Superficial oedema	18	0	21	0	22	0
Pleural effusion	18	2	24	4	28	5
Generalised oedema	3	0	4	0	4	0
Pericardial effusion	2	1	2	1	3	1
Pulmonary hypertension	0	0	0	0	2	1
Haemorrhage	11	1	11	1	12	1
Gastrointestinal bleeding	2	1	2	1	2	1

[a] Phase III dose optimisation study results reported in recommended starting dose of 100 mg once daily (n=165) population.

[b] Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as "fluid retention"

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL, the median duration of treatment was 14 months (range <1-36 months) for accelerated phase CML; 3 months (range <1-32 months) for myeloid blast CML; 4 months (<1-22 months) for lymphoid blast CML; and 3 months (<1-29 months) for Ph+ ALL. Selected adverse reactions that were reported at the recommended starting dose of 140 mg once daily are shown in Table 5. A 70 mg twice daily regimen was also studied. The 70 mg twice daily regimen showed a comparable efficacy profile to the 140 mg once daily regimen, but a less favourable safety profile.

Table 5: Selected Adverse Medicine Reactions Reported in a Phase III Dose-Optimisation Study: Advanced Phase CML and Ph+ ALL

	140mg once daily[a] n = 304	
	All Grades	**Grade 3/4**
Preferred Term		**Percent (%) of Patients**
Diarrhoea	28	3
Fluid Retention[c]	33	7
Superficial oedema	15	<1
Pleural Effusion	20	6
Generalised oedema	2	0
Congestive heart failure/cardiac dysfunctionb	1	0
Pericardial effusion	2	1
Pulmonary oedema	1	1
Ascites	0	0
Pulmonary hypertension	0	0
Haemorrhage	23	8
Gastrointestinal bleeding	8	6

[a] Phase III dose optimisation study results reported at the recommended starting dose of 140 mg once daily (n=304) population at 2 year final study follow up.[b] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.
[c] Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as "fluid retention"

The following adverse reactions were reported in patients in SPRYCEL clinical trials. 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 dysfunctiona, 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[c]
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
Metabolism and nutrition disorders
Common: appetite disturbances, 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[e], face oedema[f],fatigue, pyrexia
Common: asthenia, pain, generalised oedema[g], chest pain, chills
Uncommon: malaise, temperature intolerance, other superficial oedema[h]
Rare: gait disturbance
Immune System Disorders
Uncommon: hypersensitivity (including erythema nodosum)
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 ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure.
b. Includes cerebral hematoma, cerebral haemorrhage, extradural hematoma, haemorrhage intracranial, hemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

c. Includes medicine eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, fungal rash, generalised erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash, papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation and urticaria vesiculosa.
d. Excludes gastrointestinal bleeding and CNS bleeding; these ADRs are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.
e. Includes gravitational oedema, localised oedema, oedema peripherala
f. Includes conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face
g. includes fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema
h. includes genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling

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, pulmonary arterial hypertension
Skin and subcutaneous tissue disorders:	Stevens-Johnson syndrome[b]
Renal and urinary disorders	Nephrotic syndrome
Vascular disorders	Thrombotic microangiopathy (TMA)

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

Table 7: CTC Grades 3/4 Laboratory Abnormalities in Studies of in Patients with CML Resistant or Intolerant to Prior Imatinib Therapya

	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.

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 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of SPRYCEL (dasatinib) were evaluated in 229 healthy subjects and in 84 patients with leukaemia.

Absorption

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

Data from a study of 54 healthy subjects administered a single, 100mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects are unlikely to be clinically significant. 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 (32% and 30% 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

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

The pharmacokinetics of SPRYCEL have not been evaluated in paediatric patients.

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**).

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**)

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, platic, 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

Distributed by:

Healthcare Logistics
PO Box 62-027
Mt Wellington
Auckland, New Zealand

Phone: (09) 526 3752

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

16 August 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
5.2 Pharmacodynamic properties	Additional narrative describing dasatinib exposure variability between fasted patients and patients who have consumed light-fat or high-fat meals.

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