Sprycel 20mg, 50mg, 80mg, 100mg and 140mg Film Coated Tablets

Summary of Product Characteristics Updated 02-Apr-2015 | Bristol-Myers Squibb Pharmaceutical Limited

1. Name of the medicinal product

SPRYCEL 20 mg film-coated tablets

SPRYCEL 50 mg film-coated tablets

SPRYCEL 80 mg film-coated tablets

SPRYCEL 100 mg film-coated tablets

SPRYCEL 140 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 20 mg, 50 mg, 80 mg, 100 mg, 140 mg dasatinib (as monohydrate).

Excipients with known effect

Each 20 mg film-coated tablet contains 27 mg of lactose monohydrate.

Each 50 mg film-coated tablet contains 67.5 mg of lactose monohydrate.

Each 80 mg film-coated tablet contains 108 mg of lactose monohydrate.

Each 100 mg film-coated tablet contains 135.0 mg of lactose monohydrate.

Each 140 mg film-coated tablet contains 189 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet).

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

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

80 mg: White to off-white, biconvex, triangular film-coated tablet with "BMS 80" debossed on one side and "855" on the other side

100 mg : White to off-white, biconvex, oval film-coated tablet with "BMS 100" debossed on one side and "852" on the other side.

140 mg: White to off-white, biconvex, round film-coated tablet with "BMS 140" debossed on one side and "857" on the other side.

4. Clinical particulars

4.1 Therapeutic indications

SPRYCEL is indicated for the treatment of adult patients with:

• newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.

• chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate.

• Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

Posology

The recommended starting dose for chronic phase CML is 100 mg dasatinib once daily, administered orally.

The recommended starting dose for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 140 mg once daily, administered orally (see section 4.4).

Treatment duration

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 or

molecular response [including complete cytogenetic response (CCyR), 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, 80 mg, 100 mg and 140 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 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML or Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dose.

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 100 mg once daily)	ANC < 0.5 x 10^9/l and/or Platelets < 50 x 10^9/l	1 Stop treatment until ANC ≥ 1.0 x 10^9/l and platelets ≥ 50 x 10^9/l. 2 Resume treatment at the original starting dose. 3 If platelets < 25 x 10^9/l and/or recurrence of ANC < 0.5 x 10^9/l for > 7 days, repeat step 1 and resume treatment 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 (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated and 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 treatment 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 treatment 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-haematological adverse reaction develops with dasatinib, interrupt treatment until the event has resolved or returned to baseline. Resume at the same dose if this is the first occurrence and at a reduced dose if this is a recurrent event. If a severe grade 3 or 4, non-haematological adverse reaction develops with dasatinib, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event. For 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 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.

Pleural effusion: if a pleural effusion is diagnosed, interrupt dasatinib until patient is asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, consider a course of diuretics or corticosteroids or both concurrently (see sections 4.4 and 4.8). Following resolution of the first episode, consider reintroduction of dasatinib at the same dose level. Following resolution of a subsequent episode, reintroduce dasatinib at one dose level reduction. Following resolution of a severe (grade 3 or 4) episode, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

Paediatric population

The safety and efficacy of SPRYCEL in children and adolescents below 18 years of age have not yet been established. No data are available (see section 5.1).

Older people

No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in older people.

Hepatic impairment

Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, SPRYCEL should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2).

Renal impairment

No clinical studies were conducted with SPRYCEL in patients with decreased renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine concentration > 3 times the upper limit of the normal range, and studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration > 1.5 times the upper limit of the normal range). Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

Method of administration

SPRYCEL must be administered orally.

Film-coated tablets must not be crushed or cut in order to minimize the risk of dermal exposure, they must be swallowed whole. They can be taken with or without a meal and should be taken consistently either in the morning or in the evening.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Clinically relevant interactions

Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolized primarily by or modulate the activity of CYP3A4 (see section 4.5).

Concomitant use of dasatinib and medicinal products or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, coadministration of a potent CYP3A4 inhibitor is not recommended (see section 4.5).

Concomitant use of dasatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving dasatinib, coadministration of alternative medicinal products with less potential for CYP3A4 induction should be selected (see section 4.5).

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib is coadministered with CYP3A4 substrates of narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) (see section 4.5).

The concomitant use of dasatinib and a histamine-2 (H_2) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H_2 antagonists and proton pump inhibitors are not recommended and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib (see section 4.5).

Special populations

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see sections 4.2 and 5.2). Due to the limitations of this clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment (see section 4.2).

Important adverse reactions

Myelosuppression

Treatment with dasatinib is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In patients with advanced phase CML or Ph+ ALL, complete blood counts should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. In patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction (see sections 4.2 and 4.8).

Bleeding

In patients with chronic phase CML (n=548), 5 patients (1%) receiving dasatinib had grade 3 or 4 haemorrhage. In clinical studies in patients with advanced phase CML receiving the recommended dose of SPRYCEL (n=304), severe central nervous system (CNS) haemorrhage occurred in 1% of patients. One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 6% of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 haemorrhage occurred in 2% of patients with advanced phase CML. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopenia (see section 4.8). 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 medicinal products that inhibit platelet function or anticoagulants.

Fluid retention

Dasatinib is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, grade 3 or 4 fluid retention was reported in 13 patients (5%) in the dasatinib-treatment group and in 2 patients (1%) in the imatinib-treatment group after a minimum of 60 months follow-up (see section 4.8). In all SPRYCEL treated patients with chronic phase CML, severe fluid retention occurred in 32 patients (6%) receiving SPRYCEL at the recommended dose (n=548). In clinical studies in patients with advanced phase CML receiving SPRYCEL at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 1% of patients, respectively. In these patients grade 3 or 4 pulmonary oedema and pulmonary hypertension were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics and short courses of steroids (see sections 4.2 and 4.8). Patients aged 65 years and older are more likely than younger patients to experience pleural effusion, dyspnoea, cough, pericardial effusion and congestive heart failure, and should be monitored closely.

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib treatment (see section 4.8). In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. An echocardiography should be performed at treatment initiation in every patient presenting symptoms of cardiac disease and considered in patients with risk factors for cardiac or pulmonary disease. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for common etiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. In accordance with recommendations for management of non-haematologic adverse reactions (see section 4.2) the dose of dasatinib should be reduced or therapy interrupted during this evaluation. If no explanation is found, or if there is no improvement with dose reduction or interruption, the diagnosis of PAH should be considered. The diagnostic approach should follow standard practice guidelines. If PAH is confirmed, dasatinib should be permanently discontinued. Follow up should be performed according to standard practice guidelines. Improvements in haemodynamic and clinical parameters have been observed in dasatinib-treated patients with PAH following cessation of dasatinib therapy.

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT Interval) (see section 5.3). In 258 dasatinib-treated patients and 258 imatinib-treated patients with a minimum of 60 months follow-up in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each group had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3.0 msec in dasatinib-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1%) in each group experienced a QTcF > 500 msec. In 865 patients with leukaemia treated with dasatinib in Phase II clinical trials, the mean changes from baseline in QTc interval using Fridericia's method (QTcF) were 4 - 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec (see section 4.8).

Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one of these patients (1%) experienced a QTcF > 500 msec.

Dasatinib should be administered with caution to 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 medicinal products or other medicinal products which lead to QT prolongation, and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to dasatinib administration.

Cardiac adverse reactions

Dasatinib 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, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Adverse cardiac events were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath, and diaphoresis.

If these clinical signs or symptoms develop, physicians are advised to interrupt dasatinib administration. After resolution, a functional assessment should be performed prior to resuming treatment with dasatinib. Dasatinib may be resumed at the original dose for mild/moderate events (≤ grade 2) and resumed at a dose level reduction for severe events (≥ grade 3) (see section 4.2). Patients continuing treatment should be monitored periodically.

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

Lactose

This medicinal product contains 135 mg of lactose monohydrate in a 100 mg daily dose and 189 mg of lactose monohydrate in a 140 mg daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may increase dasatinib plasma concentrations

In vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products or substances which potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended.

At clinically relevant concentrations, binding of dasatinib to plasma proteins is approximately 96% on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicinal products. The potential for displacement and its clinical relevance are unknown.

Active substances that may decrease dasatinib plasma concentrations

When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82%. Other medicinal products that induce CYP3A4 activity (e.g. dexamethazone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John´s Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicinal products with less enzyme induction potential should be used.

Histamine-2 antagonists and proton pump inhibitors

Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. 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%. 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 use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy (see section 4.4).

Antacids

Non-clinical data demonstrate that the solubility of dasatinib is pH-dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with SPRYCEL reduced the AUC of a single dose of SPRYCEL by 55% and the C_{max} by 58%. However, when antacids were administered 2 hours prior to a single dose of SPRYCEL, no relevant changes in dasatinib concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following SPRYCEL (see section 4.4).

Active substances that may have their plasma concentrations altered by dasatinib

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In a study in healthy subjects, a single 100 mg dose of dasatinib increased AUC and C_{max} exposure to simvastatin, a known CYP3A4 substrate, by 20 and 37% respectively. It cannot be excluded that the effect is larger after multiple doses of dasatinib. Therefore, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during treatment.

Pregnancy

Based on human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3).

SPRYCEL should not be used during pregnancy unless the clinical condition of the woman requires treatment with dasatinib. If SPRYCEL is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

There is insufficient/limited information on the excretion of dasatinib in human or animal breast milk. Physico-chemical and available pharmacodynamic/toxicological data on dasatinib point to excretion in breast milk and a risk to the suckling child cannot be excluded.

Breast-feeding should be stopped during treatment with SPRYCEL.

Fertility

The effect of dasatinib on sperm is unknown, therefore both sexually active men and women should use effective methods of contraception during treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

Summary of the safety profile

The data described below reflect exposure to SPRYCEL in 2,712 patients in clinical studies, including 324 patients with newly diagnosed chronic phase CML and 2,388 patients with imatinib resistant or intolerant CML or Ph+ ALL. The median duration of therapy in 2,712 SPRYCEL treated patients was 19.2 months (range 0-93.2 months).

In the Phase III study in patients with newly diagnosed chronic phase CML with a minimum of 5 years of follow up, the median duration of therapy was approximately 60 months for both SPRYCEL (range 0.03-72.7 months) and for imatinib (range 0.3-74.6 months). The median duration of therapy in 1,618 patients with all chronic phase CML was 29 months (range 0-92.9 months). In 1,094 patients with advanced phase CML or Ph+ ALL, the median duration of treatment for patients was 6.2 months (range 0-9.32 months).

Of the 2,712 patients treated, 18% were ≥ 65 years of age, while 5% were ≥ 75 years of age.

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

In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for adverse reactions in 5% of SPRYCEL-treated patients and 4% of imatinib-treated patients with a minimum of 12 months follow-up. After a minimum of 60 months follow-up, the cumulative discontinuation rates were 14% and 7%, respectively. Among the 1,618 dasatinib-treated patients with chronic phase CML, adverse reactions leading to discontinuation were reported in 329 (20.3%) patients, and among the 1,094 dasatinib-treated patients with advanced phase disease, adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

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

Based on a minimum of 12 months follow-up the most frequently reported adverse reactions in SPRYCEL-treated patients with newly diagnosed chronic phase CML were fluid retention (including pleural effusion) (19%), diarrhoea (17%), headache (12%), rash (11%), musculoskeletal pain (11%), nausea (8%), fatigue (8%), myalgia (6%), vomiting (5%), and muscle inflammation (4%). After a minimum of 60 months follow-up the cumulative rates for rash (14%), musculoskeletal pain (14%), headache (13%), fatigue (11%), nausea (10%), myalgia (7%), vomiting (5%), and muscle inflammation or spasms (5%) increased by ≤ 3%. Cumulative rates of fluid retention and diarrhoea were 39% and 22%, respectively. 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, headache, nausea, skin rash, dyspnoea, haemorrhage, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy.

In clinical studies 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.

Tabulated summary of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in SPRYCEL clinical studies and post-marketing experience (Table 2). These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from available post-marketing data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Tabulated summary of adverse reactions	
Infections and infestations	
Very common	infection (including bacterial, viral, fungal, non-specified)
Common	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Blood and lymphatic system disorders	
Very Common	myelosuppression (including anemia, neutropenia, thrombocytopenia)
Common	febrile neutropenia
Uncommon	lymphadenopathy, lymphopenia
Rare	aplasia pure red cell
Immune system disorders	
Uncommon	hypersensitivity (including erythema nodosum)
Endocrine Disorders	
Uncommon	hypothyroidism
Rare	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
Common	appetite disturbances[a], hyperuricaemia
Uncommon	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
Rare	diabetes mellitus
Psychiatric disorders	
Common	depression, insomnia
Uncommon	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
Very common	headache
Common	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence

Uncommon	CNS bleeding*[b], syncope, tremor, amnesia, balance disorder
Rare	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
Common	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Uncommon	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
Common	tinnitus
Uncommon	hearing loss, vertigo
Cardiac disorders	
Common	congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, arrhythmia (including tachycardia), palpitations
Uncommon	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
Rare	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Not known	atrial fibrillation/atrial flutter
Vascular disorders	
Very common	haemorrhage*[d]
Common	hypertension, flushing
Uncommon	hypotension, thrombophlebitis
Rare	deep vein thrombosis, embolism, livedo reticularis
Respiratory, thoracic and mediastinal disorders	
Very common	pleural effusion*, dyspnoea
Common	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
Uncommon	pulmonary arterial hypertension, bronchospasm, asthma
Rare	pulmonary embolism, acute respiratory distress syndrome
Not known	interstitial lung disease
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain
Common	gastrointestinal bleeding*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Uncommon	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
Rare	protein-losing gastroenteropathy, ileus, anal fistula
Not known	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
Uncommon	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	

Very common	skin rash[e]
Common	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
Rare	leukocytoclastic vasculitis, skin fibrosis
Not known	Stevens-Johnson Syndrome[f]
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain
Common	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Uncommon	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
Renal and urinary disorders	
Uncommon	renal impairment (including renal failure), urinary frequency, proteinuria
Pregnancy, puerperium and perinatal conditions	
Rare	abortion
Reproductive system and breast disorders	
Uncommon	gynecomastia, menstrual disorder
General disorders and administration site conditions	
Very common	peripheral oedema[g], fatigue, pyrexia, face oedema[h]
Common	asthenia, pain, chest pain, generalised oedema*[i], chills
Uncommon	malaise, other superficial oedema[j]
Rare	gait disturbance
Investigations	
Common	weight decreased, weight increased
Uncommon	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
Common	contusion

[a] 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 and ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.

[d] Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions 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 psoriaisis, 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] 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.

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

[h] conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbitalo edema, swelling face.

[i] fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

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

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

Description of selected adverse reactions

Myelosuppression

Treatment with SPRYCEL is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (see section 4.4).

Bleeding

Bleeding drug-related events, ranging from petechiae and epistaxis to grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking SPRYCEL (see section 4.4).

Fluid retention

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

The cumulative rate of dasatinib-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, 24% at 48 months and 28% at 60 months. A total of 46 dasatinib-treated patients had recurrent pleural effusions. Seventeen patients had 2 separate events, 6 had 3 events, 18 had 4 to 8 events and 5 had > 8 episodes of pleural effusions.

The median time to first dasatinib-related grade 1 or 2 pleural effusion was 114 weeks (range: 4 to 299 weeks). Less than 10% of patients with pleural effusion had severe (grade 3 or 4) dasatinib-related pleural effusions. The median time to first occurrence of grade ≥ 3 dasatinib-related pleural effusion was 175 weeks (range: 114 to 274 weeks). The median duration of dasatinib-related pleural effusion (all grades) was 283 days (~40 weeks).

Pleural effusion was usually reversible and managed by interrupting SPRYCEL treatment and using diuretics or other appropriate supportive care measures (see sections 4.2 and 4.4). Among dasatinib-treated patients with drug-related pleural effusion (n=73), 45 (62%) had dose interruptions and 30 (41%) had dose reductions. Additionally, 34 (47%) received diuretics, 23 (32%) received corticosteroids, and 20 (27%) received both corticosteroids and diuretics. Nine (12%) patients underwent therapeutic thoracentesis.

Six percent of dasatinib-treated patients discontinued treatment due to drug-related pleural effusion.

Pleural effusion did not impair the ability of patients to obtain a response. Among the dasatinib-treated patients with pleural effusion, 96% achieved a cCCyR, 82% achieved a MMR, and 50% achieved a MR4.5 despite dose interruptions or dose adjustment.

See section 4.4 for further information on patients with chronic phase CML and advanced phase CML or Ph+ ALL.

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib exposure. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medicinal products or had co-morbidities in addition to the underlying malignancy. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following discontinuation of dasatinib.

QT Prolongation

In the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1%) of the SPRYCEL-treated patients had a QTcF > 500 msec after a minimum of 12 months follow-up (see section 4.4). No additional patients were reported to have QTcF > 500 msec after a minimum of 60 months follow-up.

In 5 Phase II clinical studies in patients with resistance or intolerance to prior imatinib therapy, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving SPRYCEL 70 mg twice daily. QT interval was corrected for heart rate by Fridericia's method. At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4 - 6 msec, with associated upper 95% confidence intervals < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received SPRYCEL in

clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF > 500 msec (see section 4.4).

Cardiac adverse reactions

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

In the Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy (median duration of treatment of 30 months), the incidence of pleural effusion and congestive heart failure/cardiac dysfunction was lower in patients treated with SPRYCEL 100 mg once daily than in those treated with SPRYCEL 70 mg twice daily. Myelosuppression was also reported less frequently in the 100 mg once daily treatment group (see Laboratory test abnormalities below). The median duration of therapy in the 100 mg once daily group was 37 months (range 1-91 months). Cumulative rates of selected adverse reactions that were reported in the 100 mg once daily recommended starting dose are shown in Table 3a.

Table 3a: Selected adverse reactions reported in a phase 3 dose optimisation study (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	27	2	28	2	28	2
Fluid Retention	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 3 dose optimisation study results reported in recommended starting dose of 100 mg once daily (n=165) population

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL, the median duration of treatment was 14 months for accelerated phase CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL. Selected adverse reactions that were reported in the recommended starting dose of 140 mg once daily are shown in Table 3b. A 70 mg twice daily regimen was also studied. The 140 mg once daily regimen showed a comparable efficacy profile to the 70 mg twice daily regimen but a more favorable safety profile.

Table 3b: Selected adverse reactions reported in phase III dose-optimisation study: Advanced Phase CML and Ph+ ALL[a]

	140 mg once daily n = 304	
	All grades	**Grade 3/4**
Preferred term	**Percent (%) of patients**	
Diarrhoea	28	3
Fluid retention	33	7
Superficial oedema	15	< 1
Pleural effusion	20	6
Generalised oedema	2	0

Congestive heart failure/ cardiac dysfunction[b]	1	0
Pericardial effusion	2	1
Pulmonary oedema	1	1
Haemorrhage	23	8
Gastrointestinal bleeding	8	6

[a] Phase 3 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.

Laboratory test abnormalities

Haematology

In the Phase III newly diagnosed chronic phase CML study, the following grade 3 or 4 laboratory abnormalities were reported after a minimum of 12 months follow-up in patients taking SPRYCEL: neutropenia (21%), thrombocytopenia (19%), and anaemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropenia, thrombocytopenia, and anaemia were 29%, 22% and 13%, respectively.

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

In patients with CML with resistance or intolerance to prior imatinib therapy, cytopenias (thrombocytopenia, neutropenia, and anaemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 4.

Table 4: CTC grades 3/4 haematological laboratory abnormalities in clinical studies in patients with resistance or intolerance to prior imatinib therapy[a]

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

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

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

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

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

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

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

Biochemistry

In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphatemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in ≤ 1% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of grade 3 or 4 hypophosphatemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained 1%. There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.

2 year follow-up

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

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

Other special population

While the safety profile of SPRYCEL in older people was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions such as fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance and more likely to experience less frequently reported adverse reactions such as abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease and should be monitored closely (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since dasatinib is associated with grade 3 or 4 myelosuppression (see section 4.4), patients who ingest more than the recommended dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01XE06

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.6-0.8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

In vitro, dasatinib is active in leukaemic cell lines representing variants of imatinib-sensitive and resistant disease. These non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations.

In vivo, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient-derived CML cell lines grown at various sites, including the central nervous system.

Clinical efficacy and safety

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

Four single-arm, uncontrolled, open-label Phase II clinical studies were conducted to determine the safety and efficacy of dasatinib in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib. One randomised non-comparative study was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose was 70 mg dasatinib twice daily. Dose modifications were allowed for improving activity or management of toxicity (see section 4.2).

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

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

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

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

Chronic Phase CML - Newly Diagnosed

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

A total of 519 patients were randomised to a treatment group: 259 to SPRYCEL and 260 to imatinib. Baseline characteristics were well balanced between the two treatment groups with respect to age (median age was 46 years for the SPRYCEL group and 49 years for the imatinib group with 10% and 11% of patients 65 years of age or older, respectively), gender (women 44% and 37%, respectively), and race (Caucasian 51% and 55%; Asian 42% and 37%, respectively). At baseline, the distribution of Hasford Scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%; intermediate risk 48% and 47%; high risk: 19% and 19%, respectively).

With a minimum of 12 months follow-up, 85% of patients randomised to the SPRYCEL group and 81% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation within 12 months due to disease progression occurred in 3% of SPRYCEL-treated patients and 5% of imatinib-treated patients.

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

Efficacy results are presented in Table 5. A statistically significantly greater proportion of patients in the SPRYCEL group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of SPRYCEL was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

Table 5: Efficacy results from a phase 3 study of newly diagnosed patients with Chronic Phase CML

	SPRYCEL n= 259	**imatinib n= 260**	**p-value**
	Response rate (95% CI)		
Cytogenetic response			
within 12 months			
cCCyR[a]	76.8% (71.2–81.8)	66.2% (60.1–71.9)	p< 0.007*
CCyR[b]	85.3% (80.4-89.4)	73.5% (67.7-78.7)	–
within 24 months			
cCCyR[a]	80.3%	74.2%	–
CCyR[b]	87.3%	82.3%	–
within 36 months			
cCCyR[a]	82.6%	77.3%	–
CCyR[b]	88.0%	83.5%	–

within 48 months			
cCCyR[a]	82.6%	78.5%	–
CCyR[b]	87.6%	83.8%	–
within 60 months			
cCCyR[a]	83.0%	78.5%	–
CCyR[b]	88.0%	83.8%	–
Major Molecular Response[c]			
12 months	52.1% (45.9–58.3)	33.8% (28.1–39.9)	p< 0.00003*
24 months	64.5% (58.3-70.3)	50% (43.8-56.2)	–
36 months	69.1% (63.1-74.7)	56.2% (49.9-62.3)	–
48 months	75.7% (70.0-80.8)	62.7% (56.5-68.6)	–
60 months	76.4% (70.8-81.5)	64.2% (58.1-70.1)	p=0.0021
	Hazard Ratio (HR)		
	within 12 months (99.99% CI)		
Time-to cCCyR	1.55 (1.0-2.3)		p< 0.0001*
Time-to MMR	2.01 (1.2-3.4)		p< 0.0001*
Durability of cCCyR	0.7 (0.4-1.4)		p< 0.035
	within 24 months (95% CI)		
Time-to cCCyR	1.49 (1.22-1.82)		–
Time-to MMR	1.69 (1.34-2.12)		–
Durability of cCCyR	0.77 (0.55-1.10)		–
	within 36 months (95% CI)		
Time-to cCCyR	1.48 (1.22-1.80)		–
Time-to MMR	1.59 (1.28-1.99)		–
Durability of cCCyR	0.77 (0.53-1.11)		–
	within 48 months (95% CI)		
Time-to cCCyR	1.45 (1.20-1.77)		–
Time-to MMR	1.55 (1.26-1.91)		–
Durability of cCCyR	0.81 (0.56-1.17)		–
	within 60 months (95% CI)		
Time-to cCCyR	1.46 (1.20-1.77)		p=0.0001
Time-to MMR	1.54 (1.25-1.89)		p<0.0001
Durability of cCCyR	0.79 (0.55-1.13)		p=0.1983

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

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

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

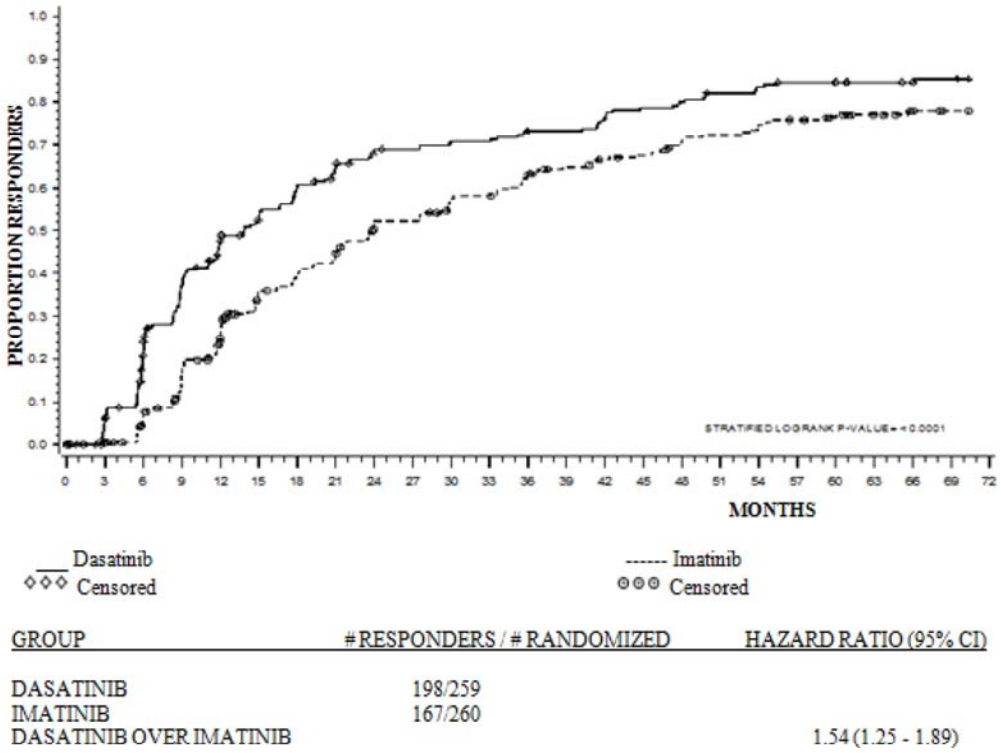
*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.

CI = confidence interval

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

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

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

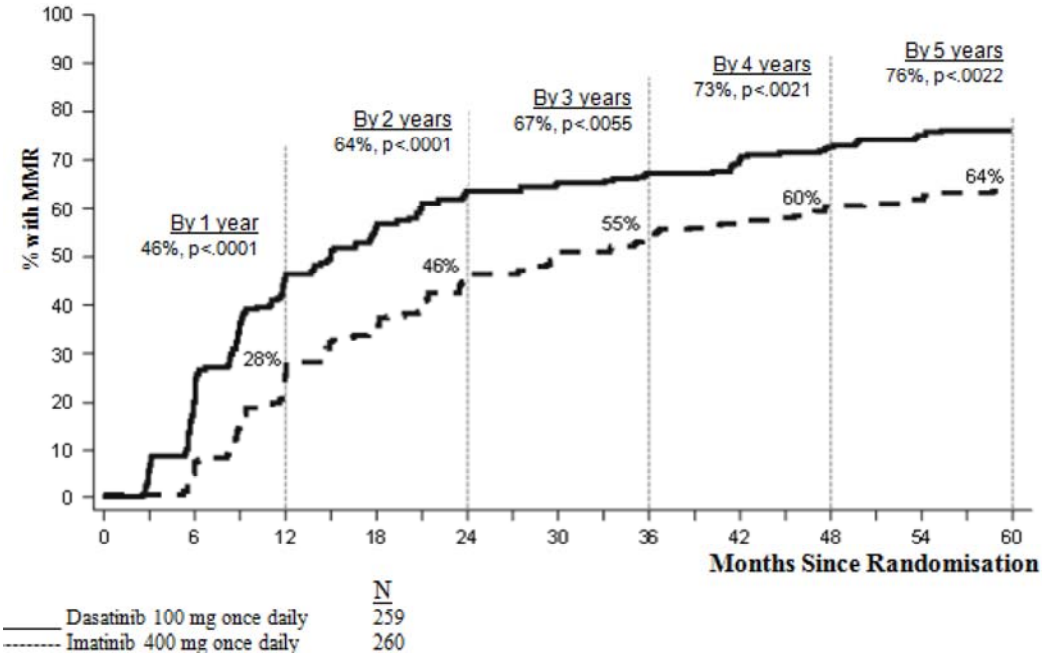


GROUP	#RESPONDERS / # RANDOMIZED	HAZARD RATIO (95% CI)
DASATINIB	198/259	
IMATINIB	167/260	
DASATINIB OVER IMATINIB		1.54 (1.25 - 1.89)

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

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

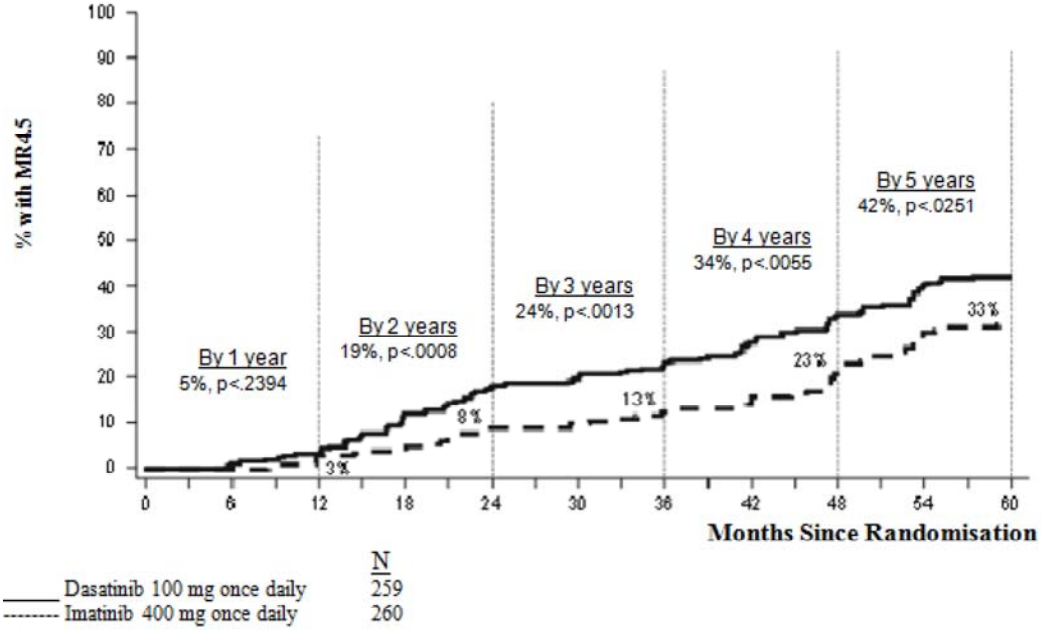
Figure 2: MMR Rates Over Time - All Randomised Patients in a Phase 3 Study of Newly Diagnosed Patients with Chronic Phase CML)



The proportion of patients achieving BCR-ABL ratio of ≤0.01% (4-log reduction) at any time was higher in the SPRYCEL group compared to the imatinib group (54.1% versus 45%). The proportion of patients achieving BCR-ABL ratio of ≤0.0032% (4.5-log reduction) at any time was higher in the SPRYCEL group compared to the imatinib group (44% versus 34%).

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

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



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

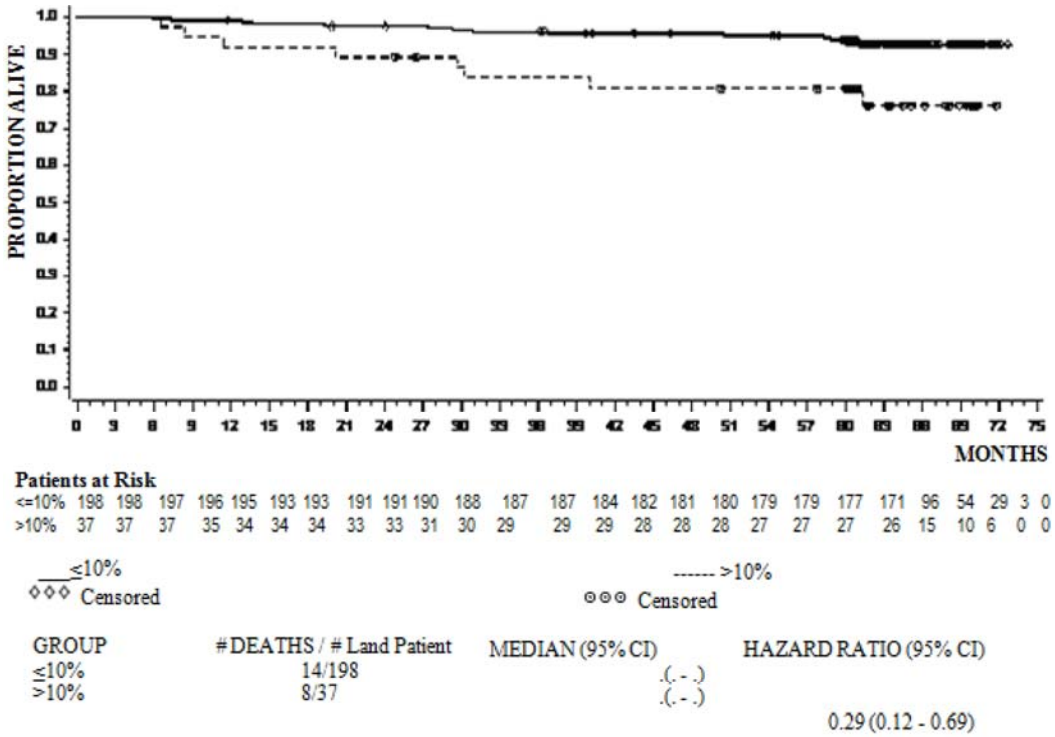
In an additional analysis, more dasatinib-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels ≤ 10% at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 6.

Table 6: Dasatinib Patients with BCR-ABL ≤ 10% and > 10% at 3 Months		
Dasatinib N = 235	**Patients with BCR-ABL ≤ 10% at 3 Months**	**Patients with BCR-ABL > 10% at 3 Months**

Number of Patients (%)	198 (84.3)	37 (15.7)
Transformation at 60 months, n/N (%)	6/198 (3.0)	5/37 (13.5)
Rate of PFS at 60 Months (95% CI)	92.0% (89.6, 95.2)	73.8% (52.0, 86.8)
Rate of OS at 60 Months (95% CI)	93.8% (89.3, 96.4)	80.6% (63.5, 90.2)

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

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



Disease progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR, partial CyR or CCyR, progression to accelerated phase or blast phase, or death. The estimated 60-month PFS rate was 88.9% (CI: 84% - 92.4%) for both the dasatinib and imatinib treatment groups. At 60 months, transformation to accelerated or blast phase occurred in fewer dasatinib-treated patients (n=8; 3%) compared with imatinib-treated patients (n=15; 5.8%). The estimated 60-month survival rates for dasatinib and imatinib-treated patients were 90.9% (CI: 86.6% - 93.8%) and 89.6% (CI: 85.2% - 92.8%), respectively. There was no difference in OS (HR 1.01, 95% CI: 0.58-1.73, p= 0.9800) and PFS (HR 1.00, 95% CI: 0.58-1.72, p = 0.9998) between dasatinib and imatinib.

In patients who report disease progression or discontinue dasatinib or imatinib therapy, BCR-ABL sequencing was performed on blood samples from patients where these are available. Similar rates of mutation were observed in both the treatment arms. The mutations detected among the dasatinib-treated patients were T315I, F317I/L and V299L. A different spectrum of mutation was detected in the imatinib treatment arm. Dasatinib does not appear to be active against the T315I mutation, based on in vitro data.

Chronic phase CML - Resistance or intolerance to prior imatinib therapy

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

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

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

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

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

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

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

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

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

A total of 387 patients received dasatinib 70 mg twice daily (288 resistant and 99 intolerant). The median time from diagnosis to start of treatment was 61 months. The majority of the patients (53%) had received prior imatinib treatment for more than 3 years. Most resistant patients (72%) had received > 600 mg imatinib. In addition to imatinib, 35% of patients had received prior cytotoxic chemotherapy, 65% had received prior interferon, and 10% had received a prior stem cell transplant. Thirty-eight percent of patients had baseline mutations known to confer imatinib resistance. Median duration of treatment on dasatinib was 24 months with 51% of patients treated for > 24 months to date. Efficacy results are reported in Table 7. MCyR was achieved in 55% of imatinib-resistant patients and 82% of imatinib-intolerant patients. With a minimum of 24 months follow-up, 21 of the 240 patients who had achieved a MCyR had progressed and the median duration of MCyR had not been reached.

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

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

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

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

Accelerated Phase CML

An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 174 patients received dasatinib 70 mg twice daily (161 resistant and 13 intolerant to imatinib). The median time from diagnosis to start of treatment was 82 months. Median duration of treatment on dasatinib was 14 months with 31% of patients treated for > 24 months to date. The rate of major molecular response (assessed in 41 patients with a CCyR) was 46% at 24 months. Further efficacy results are reported in Table 7.

Myeloid Blast Phase CML

An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 109 patients received dasatinib 70 mg twice daily (99 resistant and 10 intolerant to imatinib). The median time from diagnosis to start of treatment was 48 months. Median duration of treatment on dasatinib was 3.5 months with 12% of patients treated for > 24 months to date. The rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months. Further efficacy results are reported in Table 7.

Lymphoid Blast Phase CML and Ph+ ALL

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

Table 7: Efficacy in phase II SPRYCEL single-arm clinical studies[a]

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

Data described in this table are from studies using a starting dose of 70 mg twice daily. See section 4.2 for the recommended starting dose.

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

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

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

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

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

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

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

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

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

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

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

Efficacy was achieved across all dasatinib treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% confidence interval [-6.8% - 10.6%]); however, the 100 mg once daily regimen demonstrated improved safety and tolerability. Efficacy results are presented in Tables 8 and 9.

Table 8: Efficacy of SPRYCEL in Phase III Dose-Optimization Study: Imatinib Resistant or Intolerant Chronic Phase CML (2-year results)[a]	
All Patients	**n=167**
Imatinib-Resistant Patients	**n=124**
Hematologic Response Rate -[b]- (%) (95% CI)	
CHR	**92% (86–95)**
Cytogenetic Response -[c]- (%) (95% CI)	
MCyR	
All Patients	**63% (56–71)**
Imatinib-Resistant Patients	**59% (50–68)**
CCyR	
All Patients	**50% (42–58)**
Imatinib-Resistant Patients	**44% (35–53)**
Major Molecular Response in Patients achieving CCyR[d] (%) (95% CI)	
All Patients	**69% (58–79)**
Imatinib-Resistant Patients	**72% (58–83)**

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

[b] Hematologic response criteria (all responses confirmed after 4 weeks): Complete hematologic response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

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

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

Table 9: Long Term Efficacy of SPRYCEL in phase 3 dose optimisation study: Imatinib Resistant or Intolerant Chronic Phase CML Patients [a]				
	Minimum Follow-up Period			
	1 year	**2 years**	**5 years**	**7 years**

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

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

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

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

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

2- In the study in advanced phase CML and Ph+ ALL, the primary endpoint was MaHR. A total of 611 patients were randomised to either the dasatinib 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range 0.03-31 months).

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

Response rates are presented in Table 10.

Table 10: Efficacy of SPRYCEL in phase III dose-optimisation study: Advanced Phase CML and Ph+ ALL (2 Year Results)[a]

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

(95% CI)	(25-40)	(10-28)	(23-58)	(34-66)

[a] Results reported in recommended starting dose of 140 mg once daily (see section 4.2).

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

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

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

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

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

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

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

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

Paediatric population

Safety and efficacy of dasatinib have not yet been studied in paediatric patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with SPRYCEL in one or more subsets of the paediatric population in Philadelphia chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia and Philadelphia chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.

Absorption

Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUCτ □) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily. The overall mean terminal half-life of dasatinib is approximately 5-6 hours in patients.

Data from healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. A low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure.

Distribution

In patients, dasatinib has a large apparent volume of distribution (2,505 l) suggesting that the medicinal product is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96% on the basis of *in vitro* experiments.

Biotransformation

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product. 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 radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the dose in urine and faeces, respectively, with the remainder of the dose as metabolites.

Hepatic and renal 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 were 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 were decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function (see sections 4.2 and 4.4).

Dasatinib and its metabolites are minimally excreted via the kidney.

5.3 Preclinical safety data

The non-clinical safety profile of dasatinib was assessed in a battery of *in vitro* and *in vivo* studies in mice, rats, monkeys, and rabbits.

The primary toxicities occurred in the gastrointestinal, haematopoietic, and lymphoid systems. Gastrointestinal toxicity was dose-limiting in rats and monkeys, as the intestine was a consistent target organ. In rats, minimal to mild decreases in erythrocyte parameters were accompanied by bone marrow changes; similar changes occurred in monkeys at a lower incidence. Lymphoid toxicity in rats consisted of lymphoid depletion of the lymph nodes, spleen, and thymus, and decreased lymphoid organ weights. Changes in the gastrointestinal, haematopoietic and lymphoid systems were reversible following cessation of treatment.

Renal changes in monkeys treated for up to 9 months were limited to an increase in background kidney mineralisation. Cutaneous haemorrhage was observed in an acute, single-dose oral study in monkeys but was not observed in repeat-dose studies in either monkeys or rats. In rats, dasatinib inhibited platelet aggregation *in vitro* and prolonged cuticle bleeding time *in vivo*, but did not invoke spontaneous haemorrhage.

Dasatinib activity *in vitro* in hERG and Purkinje fiber assays suggested a potential for prolongation of cardiac ventricular repolarisation (QT interval). However, in an *in vivo* single-dose study in conscious telemetered monkeys, there were no changes in QT interval or ECG wave form.

Dasatinib was not mutagenic in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study. Dasatinib was clastogenic *in vitro* to dividing Chinese Hamster Ovary (CHO) cells.

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 embryofoetal development studies, dasatinib likewise induced embryolethality with associated decreases in litter size in rats, as well as foetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis.

In mice, dasatinib induced immunosuppression, which was dose-related and effectively managed by dose reduction and/or changes in dosing schedule. Dasatinib had phototoxic potential in an *in vitro* neutral red uptake phototoxicity assay in mouse fibroblasts. Dasatinib was considered to be non-phototoxic *in vivo* after a single oral administration to female hairless mice at exposures up to 3-fold the human exposure following administration of the recommended therapeutic dose (based on AUC).

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

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Lactose monohydrate

Cellulose, microcrystalline

Croscarmellose sodium

Hydroxypropyl cellulose

Magnesium stearate

Film-coating

Hypromellose

Titanium dioxide

Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

20 mg and 50 mg Film-coated tablets:

Alu/Alu blisters (calendar blisters or unit dose blisters).

High-density polyethylene (HDPE) bottle with child resistant closure of polypropylene.

Carton containing 56 film-coated tablets in 4 blisters of 14 film-coated tablets each.

Carton containing 60 film-coated tablets in perforated unit dose blisters.

Carton containing one bottle with 60 film-coated tablets.

80 mg, 100 mg and 140 mg Film-coated tablets:

Alu/Alu blisters (unit dose blisters).

High-density polyethylene (HDPE) bottle with child resistant closure of polypropylene.

Carton containing 30 film-coated tablets in perforated unit dose blisters.

Carton containing one bottle with 30 film-coated table

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The film-coated tablets consist of a core tablet, surrounded by a film coating to prevent exposure of health care professionals to the active substance. However, if the film-coated tablets are unintentionally 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

BRISTOL-MYERS SQUIBB PHARMA EEIG

Uxbridge Business Park

Sanderson Road

Uxbridge UB8 1DH

United Kingdom

8. Marketing authorisation number(s)

20 mg Film-coated tablets:

EU/1/06/363/004

EU/1/06/363/007

EU/1/06/363/001

50 mg Film-coated tablets:

EU/1/06/363/005

EU/1/06/363/008

EU/1/06/363/002

80 mg Film-coated tablets:

EU/1/06/363/013

EU/1/06/363/012

100 mg Film-coated tablets:

EU/1/06/363/011

EU/1/06/363/010

140 mg Film-coated tablets:

EU/1/06/363/015

EU/1/06/363/014

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 20 November 2006

Date of latest renewal: 20 November 2011

10. Date of revision of the text

19 March 2015

11. Legal category

POM

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Company Contact Details

Bristol-Myers Squibb Pharmaceutical Limited

Address

Bristol-Myers Squibb House, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH, UK

Fax

+44 (0)1895 523 010

Medical Information e-mail

medical.information@bms.com

Telephone

+44 (0)1895 523 000

Medical Information Direct Line

+44 (0) 800 731 1736

Medical Information Fax

+44 (0)1895 523 677