

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 20 mg film-coated tablets
SPRYCEL 50 mg film-coated tablets
SPRYCEL 70 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

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 80 mg film-coated tablets

Each film-coated tablet contains 80 mg dasatinib (as monohydrate).

Excipient with known effect

Each film-coated tablet contains 108 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.

SPRYCEL 140 mg film-coated tablets

Each film-coated tablet contains 140 mg dasatinib (as monohydrate).

Excipient with known effect

Each 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).

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, biconvex, oval 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 80 mg film-coated tablets

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

SPRYCEL 100 mg film-coated tablets

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

SPRYCEL 140 mg film-coated tablets

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

SPRYCEL is indicated for the treatment of paediatric patients with:

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

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

Adult patients

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

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

Paediatric population (Ph⁺ CML-CP and Ph⁺ ALL)

Dosing for children and adolescents is on the basis of body weight (see Table 1). Dasatinib is administered orally once daily in the form of either SPRYCEL film-coated tablets or SPRYCEL

powder for oral suspension (see Summary of Product Characteristics for SPRYCEL powder for oral suspension). The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with SPRYCEL treatment in children under 1 year of age.

SPRYCEL film-coated tablets and SPRYCEL powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from SPRYCEL powder for oral suspension to SPRYCEL tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so, provided that the correct dosing recommendations for the dosage form are followed.

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

Table 1: Dosage of SPRYCEL tablets for paediatric patients with Ph+ CML-CP or Ph+ ALL

Body weight (kg)^a	Daily dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

^a The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

Treatment duration

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

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

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 and powder for oral suspension (10 mg/mL suspension upon constitution). 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.

The following dose escalations shown in Table 2 are recommended in paediatric patients with Ph+ CML-CP who do not achieve a haematologic, cytogenetic and molecular response at the recommended time points, per current treatment guidelines, and who tolerate the treatment.

Table 2: Dose escalation for paediatric patients with Ph+ CML-CP

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

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

Dose adjustment for adverse reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications in adults are summarised in Table 3 and in paediatric patients with Ph+ CML-CP in Table 4. Guidelines for paediatric patients with Ph+ ALL treated in combination with chemotherapy are in a separate paragraph following the tables.

Table 3: Dose adjustments for neutropaenia and thrombocytopaenia in adults

Adults with chronic phase CML (starting dose 100 mg once daily)	ANC < 0.5 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	<ol style="list-style-type: none"> 1 Stop treatment until ANC ≥ 1.0 x 10⁹/L and platelets ≥ 50 x 10⁹/L. 2 Resume treatment at the original starting dose. 3 If platelets < 25 x 10⁹/L and/or recurrence of ANC < 0.5 x 10⁹/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).
Adults with 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	<ol style="list-style-type: none"> 1 Check if cytopaenia is related to leukaemia (marrow aspirate or biopsy). 2 If cytopaenia is unrelated to leukaemia, stop treatment until ANC ≥ 1.0 x 10⁹/L and platelets ≥ 20 x 10⁹/L and resume at the original starting dose. 3 If recurrence of cytopaenia, 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 cytopaenia is related to leukaemia, consider dose escalation to 180 mg once daily.

ANC: absolute neutrophil count

Table 4: Dose adjustments for neutropaenia and thrombocytopaenia in paediatric patients with Ph+ CML-CP

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

ANC: absolute neutrophil count

*lower tablet dose not available

For paediatric patients with Ph+ CML-CP, if Grade ≥ 3 neutropaenia or thrombocytopaenia recurs during complete haematologic response (CHR), SPRYCEL should be interrupted, and may be subsequently resumed at a reduced dose. Temporary dose reductions for intermediate degrees of cytopaenia and disease response should be implemented as needed.

For paediatric patients with Ph+ ALL, no dose modification is recommended in cases of haematologic Grade 1 to 4 toxicities. If neutropaenia and/or thrombocytopaenia result in delay of the next block of treatment by more than 14 days, SPRYCEL should be interrupted and resumed at the same dose level once the next block of treatment is started. If neutropaenia and/or thrombocytopaenia persist and the next block of treatment is delayed another 7 days, a bone marrow assessment should be performed to assess cellularity and percentage of blasts. If marrow cellularity is $<10\%$, treatment with SPRYCEL should be interrupted until ANC $>500/\mu L$ ($0.5 \times 10^9/L$), at which time treatment may be resumed at full dose. If marrow cellularity is $>10\%$, resumption of treatment with SPRYCEL may be considered.

Non-haematologic adverse reactions

If a moderate, grade 2, non-haematologic adverse reaction develops with dasatinib, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe grade 3 or 4, non-haematologic adverse reaction develops with dasatinib, treatment must be withheld until the adverse reaction has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction. 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. In CML-CP paediatric patients with non-haematologic adverse reactions, the dose reduction recommendations for haematologic adverse reactions that are described above should be followed. In Ph+ ALL paediatric patients with non-haematologic adverse reactions, if needed, one level of dose reduction should be followed, according to the dose reduction recommendations for haematologic adverse reactions that are described above.

Pleural effusion

If a pleural effusion is diagnosed, dasatinib should be interrupted until patient is examined, asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, a course of diuretics or corticosteroids or both concurrently should be considered (see

sections 4.4 and 4.8). Following resolution of the first episode, reintroduction of dasatinib at the same dose level should be considered. Following resolution of a subsequent episode, dasatinib at one dose level reduction should be reintroduced. 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 adverse reaction.

Dose reduction for concomitant use of strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with SPRYCEL should be avoided (see section 4.5). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

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

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting the dose of SPRYCEL until the CYP3A4 inhibitor is discontinued, or switching to a lower dose with the powder for oral suspension formulation (see Summary of Product Characteristics for SPRYCEL powder for oral suspension). Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

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

Special populations

Elderly

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

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 section 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.

The film-coated tablets must not be crushed, cut or chewed in order to maintain dosing consistency and minimise the risk of dermal exposure; they must be swallowed whole. Film-coated tablets should not be dispersed as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet. SPRYCEL powder for oral suspension is also available for paediatric Ph+ CML-CP and Ph+ ALL patients, and adult CML-CP patients, who cannot swallow tablets. SPRYCEL can be taken with or without a meal and should be taken consistently either in the morning or in the evening (see section 5.2). SPRYCEL should not be taken with grapefruit or grapefruit juice (see section 4.5).

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 metabolised 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 (H₂) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H₂ 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 section 5.2). Due to the limitations of this clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment.

Important adverse reactions

Myelosuppression

Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph⁺ ALL than in 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 and paediatric patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. In paediatric patients with Ph⁺ ALL treated with dasatinib in combination with chemotherapy, CBCs should be performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (see sections 4.2 and 4.8). Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction.

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 thrombocytopaenia. 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 adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopaenia (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 or Ph+ ALL 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 thoracentesis and oxygen therapy. Fluid retention adverse reactions 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. Cases of chylothorax have also been reported in patients presenting with pleural effusion (see section 4.8).

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 studies, 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 clinical study 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. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidaemia, 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 and consider the need for alternative CML-specific treatment. 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 adverse reactions (\leq grade 2) and resumed at a dose level reduction for severe adverse reactions (\geq 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.

Thrombotic microangiopathy (TMA)

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

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with SPRYCEL. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with SPRYCEL should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Effects on growth and development in paediatric patients

In paediatric trials of SPRYCEL in imatinib-resistant/intolerant Ph+ CML-CP paediatric patients and treatment-naïve Ph+ CML-CP paediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopaenia, growth retardation, and gynecomastia (see section 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

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

Growth retardation has been observed in paediatric patients treated with SPRYCEL in clinical trials (see section 4.8). Monitoring of bone growth and development in paediatric patients is recommended.

Excipients

Lactose

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total 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 (see section 4.2).

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. dexamethasone, 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. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Histamine-2 antagonists and proton pump inhibitors

Long-term suppression of gastric acid secretion by H₂ 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 H₂ 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Both sexually active men and women of childbearing potential should use effective methods of 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 foetus 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

In animal studies, the fertility of male and female rats was not affected by treatment with dasatinib (see section 5.3). Physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of SPRYCEL on fertility, and this counseling may include consideration of semen deposition.

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

Summary of the safety profile

The data described below reflect the exposure to SPRYCEL as single-agent therapy at all doses tested in clinical studies (N=2,900), including 324 adult patients with newly diagnosed chronic phase CML, 2,388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 188 paediatric patients.

In the 2,712 adult patients with either chronic phase CML, advanced phase CML or Ph+ ALL, the median duration of therapy was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1,618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months). The median duration of therapy in 1,094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months). Among 188 patients in paediatric studies, the median duration of therapy was 26.3 months (range 0 to 99.6 months). In the subset of 130 chronic phase CML SPRYCEL-treated paediatric patients, the median duration of therapy was 42.3 months (range 0.1 to 99.6 months).

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

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

Tabulated list of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients treated with SPRYCEL used as single-agent therapy in clinical studies and post-marketing experience (Table 5). These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 5: Tabulated summary of adverse reactions

Infections and infestations	
<i>Very common</i>	infection (including bacterial, viral, fungal, non-specified)
<i>Common</i>	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
<i>Not known</i>	hepatitis B reactivation
Blood and lymphatic system disorders	
<i>Very Common</i>	myelosuppression (including anaemia, neutropaenia, thrombocytopaenia)
<i>Common</i>	febrile neutropaenia
<i>Uncommon</i>	lymphadenopathy, lymphopaenia
<i>Rare</i>	aplasia pure red cell
Immune system disorders	
<i>Uncommon</i>	hypersensitivity (including erythema nodosum)
<i>Rare</i>	anaphylactic shock
Endocrine disorders	
<i>Uncommon</i>	hypothyroidism
<i>Rare</i>	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
<i>Common</i>	appetite disturbances ^a , hyperuricaemia
<i>Uncommon</i>	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
<i>Rare</i>	diabetes mellitus

Psychiatric disorders	
<i>Common</i>	depression, insomnia
<i>Uncommon</i>	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
<i>Very common</i>	headache
<i>Common</i>	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
<i>Uncommon</i>	CNS bleeding* ^b , syncope, tremor, amnesia, balance disorder
<i>Rare</i>	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
<i>Common</i>	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
<i>Uncommon</i>	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
<i>Common</i>	tinnitus
<i>Uncommon</i>	hearing loss, vertigo
Cardiac disorders	
<i>Common</i>	congestive heart failure/cardiac dysfunction* ^c , pericardial effusion*, arrhythmia (including tachycardia), palpitations
<i>Uncommon</i>	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
<i>Rare</i>	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
<i>Not known</i>	atrial fibrillation/atrial flutter
Vascular disorders	
<i>Very common</i>	haemorrhage* ^d
<i>Common</i>	hypertension, flushing
<i>Uncommon</i>	hypotension, thrombophlebitis, thrombosis
<i>Rare</i>	deep vein thrombosis, embolism, livedo reticularis
<i>Not known</i>	thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	
<i>Very common</i>	pleural effusion*, dyspnoea
<i>Common</i>	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
<i>Uncommon</i>	pulmonary arterial hypertension, bronchospasm, asthma, chylothorax*
<i>Rare</i>	pulmonary embolism, acute respiratory distress syndrome
<i>Not known</i>	interstitial lung disease
Gastrointestinal disorders	
<i>Very common</i>	diarrhoea, vomiting, nausea, abdominal pain
<i>Common</i>	gastrointestinal bleeding*, colitis (including neutropaenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
<i>Uncommon</i>	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
<i>Rare</i>	protein-losing gastroenteropathy, ileus, anal fistula
<i>Not known</i>	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
<i>Uncommon</i>	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
<i>Very common</i>	skin rash ^e
<i>Common</i>	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
<i>Uncommon</i>	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder

<i>Rare</i>	leukocytoclastic vasculitis, skin fibrosis
<i>Not known</i>	Stevens-Johnson syndrome ^f
Musculoskeletal and connective tissue disorders	
<i>Very common</i>	musculoskeletal pain ^g
<i>Common</i>	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
<i>Uncommon</i>	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
<i>Rare</i>	epiphyses delayed fusion, ^h growth retardation ^h
Renal and urinary disorders	
<i>Uncommon</i>	renal impairment (including renal failure), urinary frequency, proteinuria
<i>Not known</i>	nephrotic syndrome
Pregnancy, puerperium and perinatal conditions	
<i>Rare</i>	abortion
Reproductive system and breast disorders	
<i>Uncommon</i>	gynecomastia, menstrual disorder
General disorders and administration site conditions	
<i>Very common</i>	peripheral oedema ⁱ , fatigue, pyrexia, face oedema ^j
<i>Common</i>	asthenia, pain, chest pain, generalised oedema ^{*k} , chills
<i>Uncommon</i>	malaise, other superficial oedema ^l
<i>Rare</i>	gait disturbance
Investigations	
<i>Common</i>	weight decreased, weight increased
<i>Uncommon</i>	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
<i>Common</i>	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, erythroderma, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriasis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.

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

^g Musculoskeletal pain reported during or after discontinuing treatment.

^h Frequency reported as common in paediatric studies.

ⁱ Gravitational oedema, localised oedema, oedema peripheral.

^j Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

^k Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

^l 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, neutropaenia and thrombocytopaenia. 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 adverse reactions, 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 adverse reactions 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 adverse reactions, 6 had 3 adverse reactions, 18 had 4 to 8 adverse reactions 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.

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

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).

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (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 6a.

Table 6a: 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 6b. 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 favourable safety profile.

Table 6b: Selected adverse reactions reported in phase III dose-optimisation study: Advanced phase CML and Ph+ ALL^a

Preferred term	140 mg once daily n = 304	
	All grades	Grade 3/4
	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.

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

Of the 126 Ph+ ALL paediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in these two paediatric studies at a frequency of $\geq 10\%$ in patients on a continuous dosing regimen are shown in Table 7. Of note, pleural effusion was reported in 7 (5.6%) patients in this group, and is therefore not included in the table.

Table 7: Adverse reactions reported in $\geq 10\%$ of paediatric patients with Ph+ ALL treated with SPRYCEL on a continuous dosing regimen in combination with chemotherapy (N=126)^a

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

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

Laboratory test abnormalities

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: neutropaenia (21%), thrombocytopaenia (19%), and anaemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropaenia, thrombocytopaenia, 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, cytopaenias (thrombocytopaenia, neutropaenia, and anaemia) were a consistent finding. However, the occurrence of cytopaenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 8.

Table 8: CTC grades 3/4 haematological laboratory abnormalities in clinical studies in patients with resistance or intolerance to prior imatinib therapy^a

patients with resistance or intolerance to prior imatinib therapy				
	Chronic phase (n= 165) ^b	Accelerated phase (n= 157) ^c	Myeloid blast phase (n= 74) ^c	Lymphoid blast phase and Ph+ ALL (n= 168) ^c
	Percent (%) of patients			
Haematology parameters				
Neutropaenia	36	58	77	76
Thrombocytopaenia	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: neutropaenia (Grade 3 $\geq 0.5 - < 1.0 \times 10^9/l$, Grade 4 $< 0.5 \times 10^9/l$); thrombocytopaenia (Grade 3 $\geq 25 - < 50 \times 10^9/l$, Grade 4 $< 25 \times 10^9/l$); anaemia (haemoglobin Grade 3 $\geq 65 - < 80$ g/l, Grade 4 < 65 g/l).

Cumulative grade 3 or 4 cytopaenias among patients treated with 100 mg once daily were similar at 2 and 5 years including: neutropaenia (35% vs. 36%), thrombocytopaenia (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 hypophosphataemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in $\leq 1\%$ 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 hypophosphataemia 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 $\leq 1\%$ 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 hypophosphataemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in < 1% of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.

Paediatric population

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

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

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

Special population

While the safety profile of SPRYCEL in elderly 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 national reporting system listed in [Appendix V](#).

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 agents, protein kinase inhibitors, ATC code: L01EA02

Pharmacodynamics

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 PDGF β 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.

Mechanism of action

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, multicentre, 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 9. 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 9: 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 $\leq 0.1\%$ by RQ PCR in peripheral blood samples standardised on the International scale. These are cumulative rates representing minimum follow up for the timeframe specified.

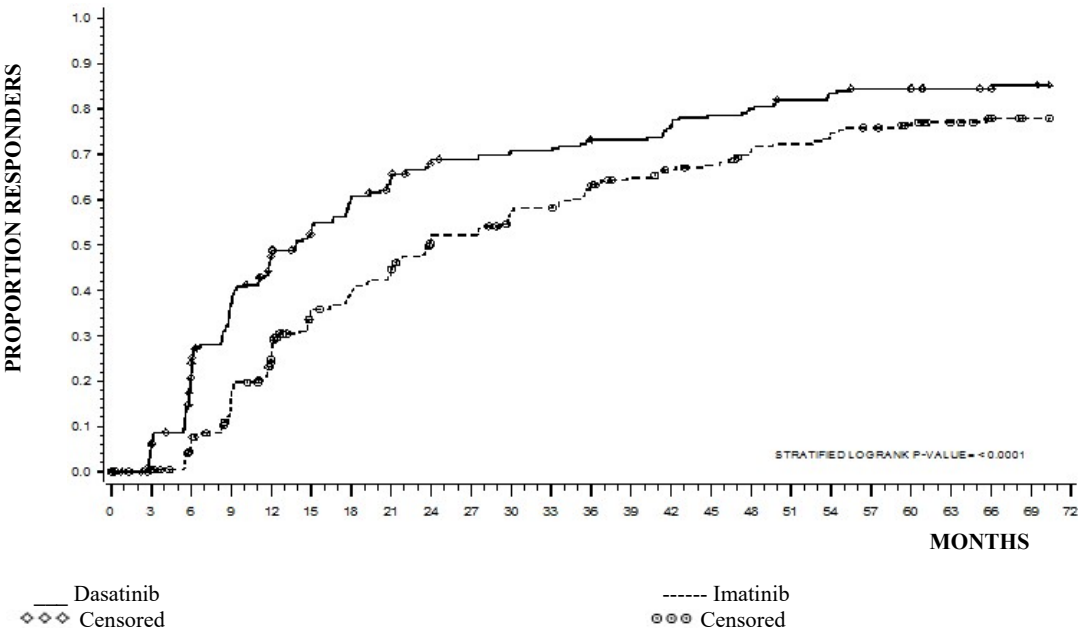
*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.

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)

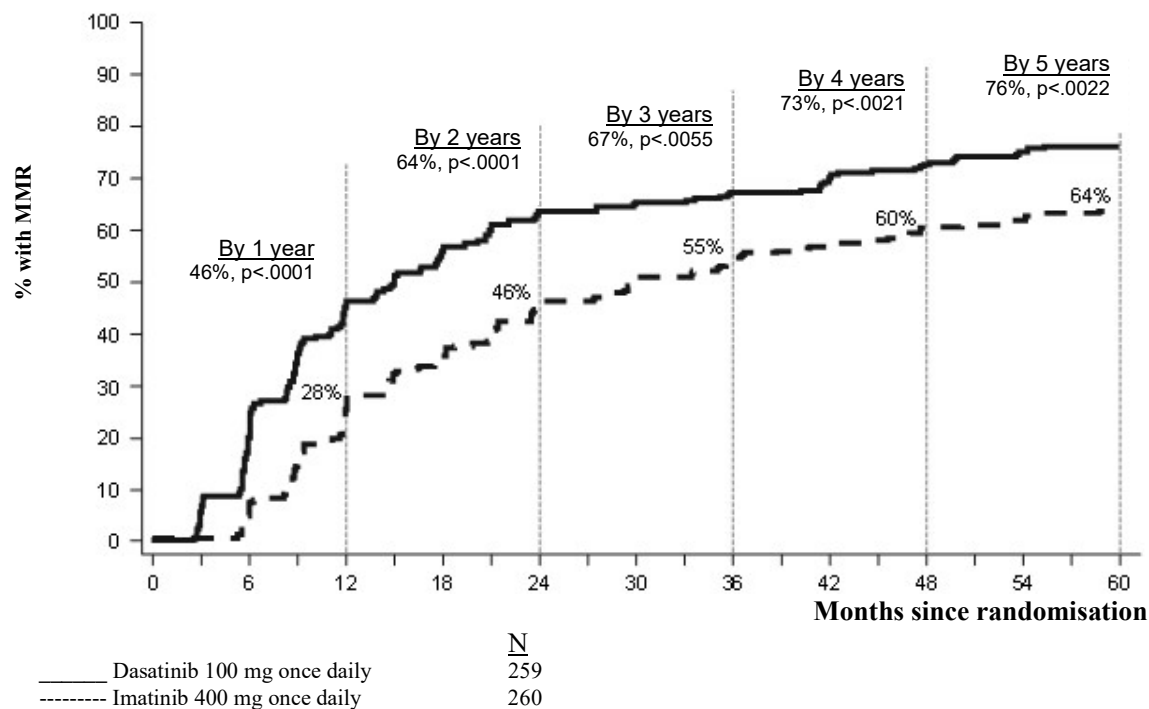


GROUP	# RESPONDERS / # RANDOMIZED	HAZARD RATIO (95% CI)
Dasatinib	198/259	
Imatinib	167/260	
Dasatinib over imatinib		1.54 (1.25 - 1.89)

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 time point are displayed graphically in Figure 2. Rates of MMR were consistently higher in dasatinib-treated patients compared with imatinib-treated patients.

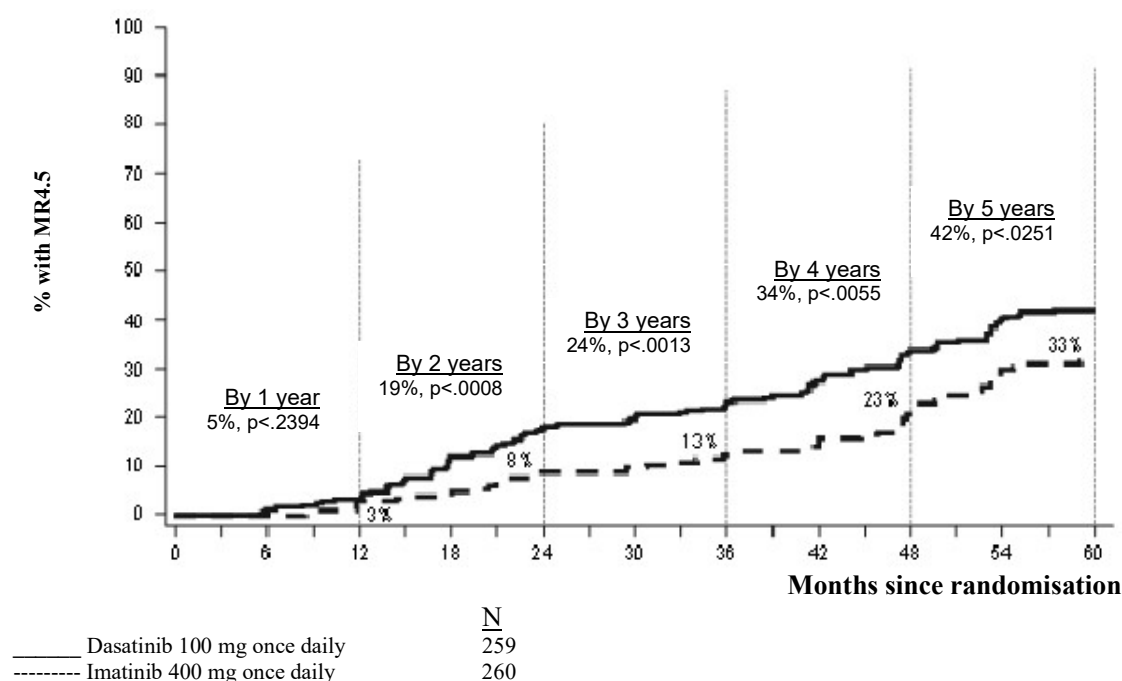
Figure 2: MMR rates over time - all randomised patients in a phase 3 study of newly diagnosed patients with chronic phase CML



The proportion of patients achieving BCR-ABL ratio of $\leq 0.01\%$ (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 $\leq 0.0032\%$ (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 are displayed graphically in Figure 3. Rates of MR4.5 over time were 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).

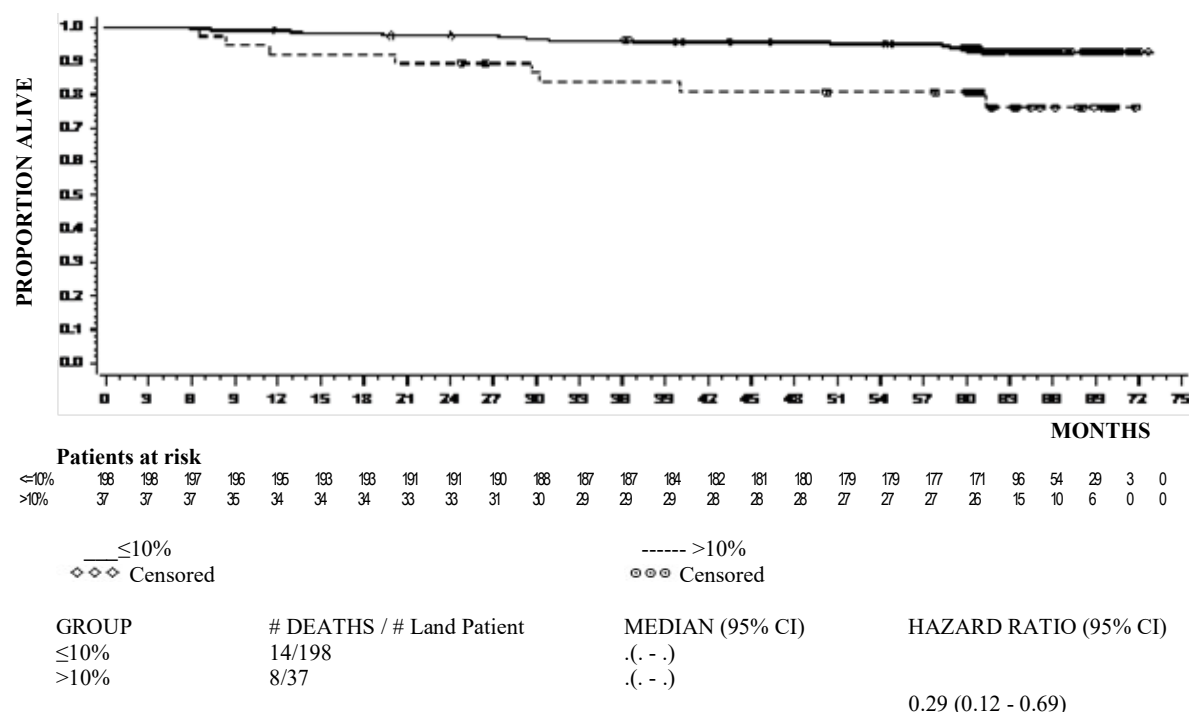
In an additional analysis, more dasatinib-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels $\leq 10\%$ at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free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

Table 10: Dasatinib patients with BCR-ABL $\leq 10\%$ and $> 10\%$ at 3 months

Dasatinib N = 235	Patients with BCR-ABL $\leq 10\%$ 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 time point is displayed graphically in Figure 4. Rate of OS was consistently higher in dasatinib treated patients who achieved BCR-ABL level $\leq 10\%$ at 3 months than those who did not.

Figure 4: Landmark plot for overall survival for dasatinib by BCR-ABL level ($\leq 10\%$ 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).

Study 1

An open-label, randomised, non-comparative multicentre 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 $\leq 0.1\%$ by RQ-PCR in peripheral blood samples) prior to crossover was 29% for dasatinib and 12% for imatinib.

Study 2

An open-label, single-arm, multicentre 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 11. 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, multicentre 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 11.

Myeloid blast phase CML

An open-label, single-arm, multicentre 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 11.

Lymphoid blast phase CML and Ph+ ALL

An open-label, single-arm, multicentre 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 11. 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 11: 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/mm³, 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/mm³, platelets ≥ 100,000/mm³, 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/mm³ and < 1,000/mm³, or platelets ≥ 20,000/mm³ and ≤ 100,000/mm³.

^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.

Study 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 12 and 13.

Table 12: 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
Haematologic response^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 Haematologic response criteria (all responses confirmed after 4 weeks): Complete haematologic response (CHR) (chronic CML): WBC \leq institutional ULN, platelets $<450,000/\text{mm}^3$, 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 $\leq 0.1\%$ by RQ-PCR in peripheral blood samples

Table 13: 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, $\geq 30\%$ 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%.

Study 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 14.

Table 14: 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	66%	28%	42%	38%
(95% CI)	(59-74)	(18-40)	(26-61)	(23-54)
CHR^b	47%	17%	21%	33%
(95% CI)	(40-56)	(10-28)	(9-39)	(19-49)
NEL^b	19%	11%	21%	5%
(95% CI)	(13-26)	(5-20)	(9-39)	(1-17)
MCyR^c	39%	28%	52%	70%
(95% CI)	(31-47)	(18-40)	(34-69)	(54-83)
CCyR	32%	17%	39%	50%
(95% CI)	(25-40)	(10-28)	(23-58)	(34-66)

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

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

CHR: WBC ≤ institutional ULN, ANC ≥ 1,000/mm³, platelets ≥ 100,000/mm³, 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/mm³ and < 1,000/mm³, or platelets ≥ 20,000/mm³ and ≤ 100,000/mm³.

^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

Paediatric patients with CML

Among 130 patients with chronic phase CML (CML-CP) treated in two paediatric studies, a Phase I, open-label, nonrandomized dose-ranging trial and a Phase II, open-label, nonrandomized trial, 84 patients (exclusively from the Phase II trial) were newly diagnosed with CML-CP and 46 patients (17 from the Phase I trial and 29 from the Phase II trial) were resistant or intolerant to previous treatment with imatinib. Ninety-seven of the 130 paediatric patients with CML-CP were treated with SPRYCEL tablets 60 mg/m² once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Key efficacy endpoints were: complete cytogenetic response (CCyR), major cytogenetic response (MCyR) and major molecular response (MMR). Results are shown in Table 15.

Table 15: Efficacy of SPRYCEL in paediatric patients with CML-CP
Cumulative response over time by minimum follow-up period

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

^a Patients from Phase II paediatric study of newly diagnosed CML-CP receiving oral tablet formulation

^b Patients from Phase I and Phase II paediatric studies of imatinib-resistant or intolerant CML-CP receiving oral tablet formulation

In the Phase I paediatric study, after a minimum of 7 years of follow-up among the 17 patients with imatinib-resistant or intolerant CML-CP, the median duration of PFS was 53.6 months and the rate of OS was 82.4%.

In the Phase II paediatric study, in patients receiving the tablet formulation, estimated 24-month PFS rate among the 51 patients with newly diagnosed CML-CP was 94.0% (82.6, 98.0), and 81.7% (61.4, 92.0) among the 29 patients with imatinib-resistant/intolerant CML-CP. After 24 months of follow-up, OS in newly diagnosed patients was 100%, and 96.6% in imatinib-resistant or intolerant patients. In the Phase II paediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or intolerant patients progressed to blast phase CML.

There were 33 newly diagnosed paediatric patients with CML-CP who received SPRYCEL powder for oral suspension at a dose of 72 mg/m². This dose represents 30% lower exposure compared to the recommended dose (see section 5.2. of Summary of Product Characteristics for SPRYCEL powder for oral suspension). In these patients, CCyR and MMR were CCyR: 87.9% [95% CI: (71.8-96.6)] and MMR: 45.5% [95% CI: (28.1-63.6)] at 12 months.

Among dasatinib-treated CML-CP paediatric patients previously exposed to imatinib, the mutations detected at the end of treatment were: T315A, E255K and F317L. However, E255K and F317L were also detected prior to treatment. There were no mutations detected in newly diagnosed CML-CP patients at the end of treatment.

Paediatric patients with ALL

The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a pivotal study in paediatric patients over one year of age with newly diagnosed Ph+ ALL.

In this multicenter, historically-controlled Phase II study of dasatinib added to standard chemotherapy, 106 paediatric patients with newly diagnosed Ph+ ALL, of whom 104 patients had confirmed Ph+ ALL, received dasatinib at a daily dose of 60 mg/m² on a continuous dosing regimen for up to 24 months, in combination with chemotherapy. Eighty-two patients received dasatinib tablets exclusively and 24 patients received dasatinib powder for oral suspension at least once, 8 of whom received dasatinib powder for oral suspension exclusively. The backbone chemotherapy regimen was the same as used in the AIEOP-BFM ALL 2000 trial (chemotherapeutic standard multi-agent chemotherapy protocol). The primary efficacy endpoint was 3-year event-free survival (EFS), which was 65.5% (55.5, 73.7).

The minimal residual disease (MRD) negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

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 (AUC_t) 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. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

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

Distribution

In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV% 93%), 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 [¹⁴C]-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

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [¹⁴C]-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.

Paediatric population

The pharmacokinetics of dasatinib have been evaluated in 104 paediatric patients with leukaemia or solid tumours (72 who received the tablet formulation and 32 who received the powder for oral suspension).

In a paediatric pharmacokinetics study, dose-normalized dasatinib exposure (C_{avg} , C_{min} and C_{max}) appears similar between 21 patients with CP-CML and 16 patients with Ph+ ALL.

Pharmacokinetics of the tablet formulation of dasatinib were evaluated for 72 paediatric patients with relapsed or refractory leukaemia or solid tumours at oral doses ranging from 60 to 120 mg/m² once daily and 50 to 110 mg/m² twice daily. Data was pooled across two studies and showed that dasatinib was rapidly absorbed. Mean T_{max} was observed between 0.5 and 6 hours and mean half-life ranged from 2 to 5 hours across all dose levels and age groups. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in paediatric patients. There was no significant difference of dasatinib PK between children and adolescents. The geometric means of dose-normalized dasatinib C_{max} , AUC (0-T), and AUC (INF) appeared to be similar between children and adolescents at different dose levels. A PPK model-based simulation predicted that the body weight tiered dosing recommendation described for the tablet, in section 4.2, is expected to provide similar exposure to a tablet dose of 60 mg/m². These data should be considered if patients are to switch from tablets to powder for oral suspension or vice versa.

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 embryoletality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryoletality 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
Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropylcellulose
Magnesium stearate

Film-coating

Hypromellose
Titanium dioxide (E171)
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

SPRYCEL 20 mg, SPRYCEL 50 mg and SPRYCEL 70 mg film-coated tablets

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

HDPE bottle with a polypropylene child-resistant closure.

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

Carton containing 60 x 1 film-coated tablets in perforated unit dose blisters.

Carton containing one bottle with 60 film-coated tablets.

SPRYCEL 80 mg, SPRYCEL 100 mg and SPRYCEL 140 mg film-coated tablets

Alu/Alu blisters (perforated unit dose blisters).

HDPE bottle with a polypropylene child-resistant closure.

Carton containing 30 x 1 film-coated tablets in perforated unit dose blisters.

Carton containing one bottle with 30 film-coated tablets.

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 healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, 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
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBERS

SPRYCEL 20 mg film-coated tablets

EU/1/06/363/004

EU/1/06/363/007

EU/1/06/363/001

SPRYCEL 50 mg film-coated tablets

EU/1/06/363/005

EU/1/06/363/008

EU/1/06/363/002

SPRYCEL 70 mg film-coated tablets

EU/1/06/363/006

EU/1/06/363/009

EU/1/06/363/003

SPRYCEL 80 mg film-coated tablets

EU/1/06/363/013

EU/1/06/363/012

SPRYCEL 100 mg film-coated tablets

EU/1/06/363/011

EU/1/06/363/010

SPRYCEL 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: 15 July 2016

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 10 mg/mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One bottle of powder for oral suspension contains 990 mg of dasatinib (as monohydrate). After constitution, one bottle contains 99 mL of oral suspension. Each mL of oral suspension contains 10 mg of dasatinib (as monohydrate).

Excipient with known effect

Each mL of oral suspension contains approximately 291 mg of sucrose, 2.1 mg of sodium, 0.25 mg of sodium benzoate, 0.25 mg of benzoic acid, 0.017 mg of benzyl alcohol and <10 ppm of sulphur dioxide (E220).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SPRYCEL is indicated for the treatment of paediatric patients with:

- newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ acute lymphoblastic leukaemia (ALL) in combination with chemotherapy.

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

Dosing is on the basis of body weight (see Table 1). Dasatinib is administered orally once daily in the form of either SPRYCEL powder for oral suspension or film-coated tablets (see Summary of Product Characteristics for SPRYCEL film-coated tablets). The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with SPRYCEL treatment in children under 1 year of age.

SPRYCEL film-coated tablets and SPRYCEL powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from SPRYCEL powder for oral suspension to SPRYCEL tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so, provided that the correct dosing recommendations for the dosage form are followed.

The recommended starting daily dosage of SPRYCEL powder for oral suspension for paediatric patients with Ph+ CML-CP or Ph+ ALL and adult patients with Ph+ CML-CP who cannot swallow tablets is shown in Table 1.

Table 1: Dosage of SPRYCEL powder for oral suspension for patients with Ph+ CML-CP and paediatric patients with Ph+ ALL (10 mg/mL suspension upon constitution)

Body weight (kg)	Daily dose, mL (mg)
5 to less than 10 kg	4 mL (40 mg)
10 to less than 20 kg	6 mL (60 mg)
20 to less than 30 kg	9 mL (90 mg)
30 to less than 45 kg	10.5 mL (105 mg)
at least 45 kg	12 mL (120 mg)

The dose for the use of powder for oral suspension in adult patients with accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL has not been determined.

Treatment duration

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

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

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 and powder for oral suspension (10 mg/mL suspension upon constitution). Dose increase or reduction is recommended based on patient response and tolerability.

Dose escalation

The following dose escalations shown in Table 2 are recommended in paediatric patients with Ph+ CML-CP who do not achieve a haematologic, cytogenetic and molecular response at the recommended time points, per current treatment guidelines, and who tolerate the treatment.

Table 2: Dose escalation for patients with Ph+ CML-CP

	Dose (maximum dose per day)	
	Starting dose	Escalation
Powder for oral suspension	4 mL (40 mg)	5 mL (50 mg)
	6 mL (60 mg)	8 mL (80 mg)
	9 mL (90 mg)	12 mL (120 mg)
	10.5 mL (105 mg)	14 mL (140 mg)
	12 mL (120 mg)	16 mL (160 mg)

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

Dose adjustment for adverse reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications in paediatric patients with CML-CP are summarised in Table 3. Guidelines for paediatric patients with Ph+ ALL treated in combination with chemotherapy are in a separate paragraph following the table.

Table 3: Dose adjustments for neutropaenia and thrombocytopaenia in paediatric patients with Ph+ CML-CP

1. If cytopaenia persists for more than 3 weeks, check if cytopaenia is related to leukaemia (marrow aspirate or biopsy).	Dose (maximum dose per day)			
		Original starting dose	One-level dose reduction	Two-level dose reduction
2. If cytopaenia is unrelated to leukaemia, stop treatment until $ANC \geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ and resume at the original starting dose or at a reduced dose.	Powder for oral suspension	4 mL (40 mg)	3 mL (30 mg)	2 mL (20 mg)
		6 mL (60 mg)	5 mL (50 mg)	4 mL (40 mg)
		9 mL (90 mg)	7 mL (70 mg)	6 mL (60 mg)
		10.5 mL (105 mg)	9 mL (90 mg)	7 mL (70 mg)
		12 mL (120 mg)	10 mL (100 mg)	8 mL (80 mg)
3. If cytopaenia recurs, repeat marrow aspirate/biopsy and resume treatment at a reduced dose.				

ANC: absolute neutrophil count

For paediatric patients with Ph+ CML-CP, if Grade ≥ 3 neutropaenia or thrombocytopaenia recurs during complete haematologic response (CHR), SPRYCEL should be interrupted, and may be subsequently resumed at a reduced dose. Temporary dose reductions for intermediate degrees of cytopaenia and disease response should be implemented as needed.

For paediatric patients with Ph+ ALL, no dose modification is recommended in cases of haematologic Grade 1 to 4 toxicities. If neutropaenia and/or thrombocytopaenia result in delay of the next block of treatment by more than 14 days, SPRYCEL should be interrupted and resumed at the same dose level once the next block of treatment is started. If neutropaenia and/or thrombocytopaenia persist and the next block of treatment is delayed another 7 days, a bone marrow assessment should be performed to assess cellularity and percentage of blasts. If marrow cellularity is $<10\%$, treatment with SPRYCEL should be interrupted until $ANC > 500/\mu L$ ($0.5 \times 10^9/L$), at which time treatment may be resumed at full dose. If marrow cellularity is $>10\%$, resumption of treatment with SPRYCEL may be considered.

Non-haematologic adverse reactions

If a moderate, grade 2, non-haematologic adverse reaction develops with dasatinib, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe grade 3 or 4, non-haematologic adverse reaction develops with dasatinib, treatment must be withheld until the adverse reaction has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction. In CML-CP paediatric patients with non-haematologic adverse reactions, the dose reduction recommendations for haematologic adverse reactions that are described above should be followed. In Ph+ ALL paediatric patients with non-haematologic adverse reactions, if needed, one level of dose

reduction should be followed, according to the dose reduction recommendations for haematologic adverse reactions that are described above.

Pleural effusion

If a pleural effusion is diagnosed, dasatinib should be interrupted until patient is examined, asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, a course of diuretics or corticosteroids or both concurrently should be considered (see sections 4.4 and 4.8). Following resolution of the first episode, reintroduction of dasatinib at the same dose level should be considered. Following resolution of a subsequent episode, dasatinib at one dose level reduction should be reintroduced. 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 adverse reaction.

Dose reduction for concomitant use of strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with SPRYCEL should be avoided (see section 4.5). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

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

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting the dose of SPRYCEL until the CYP3A4 inhibitor is discontinued, or switching to a lower dose with the powder for oral suspension formulation. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

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

Guidelines for dose reduction for paediatric patients in whom SPRYCEL powder for oral suspension must be administered with a strong CYP3A4 inhibitor are shown in Table 4.

Table 4: Dose reduction for concomitant use of strong CYP3A4 inhibitors in paediatric patients

Body weight (kg)	Dose	
	Original dose	Dose reduction
Powder for oral suspension		
5 to less than 10	4 mL (40 mg)	1 mL (10 mg)
10 to less than 20	6 mL (60 mg)	1 mL (10 mg)
20 to less than 30	9 mL (90 mg)	2 mL (20 mg)
30 to less than 45	10.5 mL (105 mg)	2 mL (20 mg)
at least 45	12 mL (120 mg)	2.5 mL (25 mg)

Special populations

Elderly

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

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 section 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. It can be taken with or without a meal and should be taken consistently either in the morning or in the evening (see section 5.2). The oral suspension should not be taken with grapefruit or grapefruit juice (see section 4.5). Constituted oral suspension may be further mixed with milk, yogurt, apple juice, or applesauce.

For details on preparation and administration of this medicinal product and instructions for use, see section 6.6.

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 metabolised 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 (H₂) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H₂ 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 section 5.2). Due to the

limitations of this clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment.

Important adverse reactions

Myelosuppression

Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in 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 and paediatric patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. In paediatric patients with Ph+ ALL treated with dasatinib in combination with chemotherapy, CBCs should be performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (see sections 4.2 and 4.8). Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction.

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 thrombocytopaenia. 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 adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopaenia (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 or Ph+ ALL 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 adverse reactions 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. Cases of chylothorax have also been reported in patients presenting with pleural effusion (see section 4.8).

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 studies, 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 clinical study 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. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidaemia, 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 and consider the need for alternative CML-specific treatment. 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 adverse reactions (\leq grade 2) and resumed at a dose level reduction for severe adverse reactions (\geq 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.

Thrombotic microangiopathy (TMA)

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

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with SPRYCEL. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with SPRYCEL should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Effects on growth and development in paediatric patients

In paediatric trials of SPRYCEL in imatinib-resistant/intolerant Ph+ CML-CP paediatric patients and treatment-naïve Ph+ CML-CP paediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopaenia, growth retardation, and gynecomastia (see section 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

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

Growth retardation has been observed in paediatric patients treated with SPRYCEL in clinical trials (see section 4.8). Monitoring of bone growth and development in paediatric patients is recommended.

Excipients

Sodium

This medicinal product contains 2.1 mg sodium per mL of SPRYCEL oral suspension. At the maximum daily dose of 16 mL oral suspension, this is equivalent to 1.7% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

Sucrose

SPRYCEL powder for oral suspension contains approximately 0.29 g/mL of sucrose upon constitution with water. For the recommended paediatric dosage, SPRYCEL oral suspension contains 1.17 grams sucrose per 40 mg dasatinib and 4.37 grams sucrose per 150 mg dasatinib. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

May be harmful to the teeth.

Benzoic acid and benzoates

SPRYCEL contains 0.25 mg benzoic acid in each mL of oral suspension and 0.25 mg sodium benzoate in each mL of oral suspension.

Benzoic acid/Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

Benzyl alcohol

SPRYCEL contains 0.017 mg benzyl alcohol in each mL of oral suspension. Benzyl alcohol may cause allergic reactions.

Monitor patients less than 3 years of age for respiratory symptoms.

SPRYCEL should not be used during pregnancy unless the clinical condition of the woman requires treatment with dasatinib (see section 4.6). Advise patients who are or may become pregnant of the potential risk to the foetus from dasatinib and the excipient benzyl alcohol, which may accumulate over time and cause metabolic acidosis.

Use with caution in patients with hepatic or renal impairment, as benzyl alcohol may accumulate over time and cause metabolic acidosis.

Sulphur dioxide (E220)

May rarely cause severe hypersensitivity reactions and bronchospasm.

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 potentially 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 (see section 4.2).

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. dexamethasone, 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. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Histamine-2 antagonists and proton pump inhibitors

Long-term suppression of gastric acid secretion by H₂ 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 H₂ 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, pimozone, 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Both sexually active men and women of childbearing potential should use effective methods of 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 foetus 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.

Pregnant or breast-feeding women should avoid exposure to SPRYCEL powder for oral suspension.

Fertility

In animal studies, the fertility of male and female rats was not affected by treatment with dasatinib (see section 5.3). Physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of SPRYCEL on fertility, and this counseling may include consideration of semen deposition.

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

Summary of the safety profile

The data described below reflect the exposure to SPRYCEL as single-agent therapy at all doses tested in clinical studies (N=2,900), including 324 adult patients with newly diagnosed chronic phase CML, 2,388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 188 paediatric patients.

In the 2,712 adult patients with either chronic phase CML, advanced phase CML or Ph+ ALL, the median duration of therapy was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1,618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months). The median duration of therapy in 1,094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months). Among 188 patients in paediatric studies, the median duration of therapy was 26.3 months (range 0 to 99.6 months). In the subset of 130 chronic phase CML SPRYCEL-treated paediatric patients, the median duration of therapy was 42.3 months (range 0.1 to 99.6 months).

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

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

Tabulated list of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients treated with SPRYCEL used as single-agent therapy in clinical studies and post-marketing experience (Table 5). These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 5: Tabulated summary of adverse reactions

Infections and infestations	
<i>Very common</i>	infection (including bacterial, viral, fungal, non-specified)
<i>Common</i>	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
<i>Not known</i>	hepatitis B reactivation
Blood and lymphatic system disorders	
<i>Very Common</i>	myelosuppression (including anaemia, neutropaenia, thrombocytopaenia)
<i>Common</i>	febrile neutropaenia
<i>Uncommon</i>	lymphadenopathy, lymphopaenia
<i>Rare</i>	aplasia pure red cell
Immune system disorders	
<i>Uncommon</i>	hypersensitivity (including erythema nodosum)
<i>Rare</i>	anaphylactic shock
Endocrine disorders	
<i>Uncommon</i>	hypothyroidism
<i>Rare</i>	hyperthyroidism, thyroiditis

Metabolism and nutrition disorders	
<i>Common</i>	appetite disturbances ^a , hyperuricaemia
<i>Uncommon</i>	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
<i>Rare</i>	diabetes mellitus
Psychiatric disorders	
<i>Common</i>	depression, insomnia
<i>Uncommon</i>	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
<i>Very common</i>	headache
<i>Common</i>	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
<i>Uncommon</i>	CNS bleeding ^{*b} , syncope, tremor, amnesia, balance disorder
<i>Rare</i>	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
<i>Common</i>	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
<i>Uncommon</i>	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
<i>Common</i>	tinnitus
<i>Uncommon</i>	hearing loss, vertigo
Cardiac disorders	
<i>Common</i>	congestive heart failure/cardiac dysfunction ^{*c} , pericardial effusion*, arrhythmia (including tachycardia), palpitations
<i>Uncommon</i>	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
<i>Rare</i>	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
<i>Not known</i>	atrial fibrillation/atrial flutter
Vascular disorders	
<i>Very common</i>	haemorrhage ^{*d}
<i>Common</i>	hypertension, flushing
<i>Uncommon</i>	hypotension, thrombophlebitis, thrombosis
<i>Rare</i>	deep vein thrombosis, embolism, livedo reticularis
<i>Not known</i>	thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	
<i>Very common</i>	pleural effusion*, dyspnoea
<i>Common</i>	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
<i>Uncommon</i>	pulmonary arterial hypertension, bronchospasm, asthma, chylothorax*
<i>Rare</i>	pulmonary embolism, acute respiratory distress syndrome
<i>Not known</i>	interstitial lung disease
Gastrointestinal disorders	
<i>Very common</i>	diarrhoea, vomiting, nausea, abdominal pain
<i>Common</i>	gastrointestinal bleeding*, colitis (including neutropaenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
<i>Uncommon</i>	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
<i>Rare</i>	protein-losing gastroenteropathy, ileus, anal fistula
<i>Not known</i>	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
<i>Uncommon</i>	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
<i>Very common</i>	skin rash ^e
<i>Common</i>	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria,

	hyperhidrosis
<i>Uncommon</i>	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
<i>Rare</i>	leukocytoclastic vasculitis, skin fibrosis
<i>Not known</i>	Stevens-Johnson syndrome ^f
Musculoskeletal and connective tissue disorders	
<i>Very common</i>	musculoskeletal pain ^g
<i>Common</i>	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
<i>Uncommon</i>	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
<i>Rare</i>	epiphyses delayed fusion, ^h growth retardation ^h
Renal and urinary disorders	
<i>Uncommon</i>	renal impairment (including renal failure), urinary frequency, proteinuria
<i>Not known</i>	nephrotic syndrome
Pregnancy, puerperium and perinatal conditions	
<i>Rare</i>	abortion
Reproductive system and breast disorders	
<i>Uncommon</i>	gynecomastia, menstrual disorder
General disorders and administration site conditions	
<i>Very common</i>	peripheral oedema, ⁱ fatigue, pyrexia, face oedema ^j
<i>Common</i>	asthenia, pain, chest pain, generalised oedema ^{*k} , chills
<i>Uncommon</i>	malaise, other superficial oedema ^l
<i>Rare</i>	gait disturbance
Investigations	
<i>Common</i>	weight decreased, weight increased
<i>Uncommon</i>	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
<i>Common</i>	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, erythroderma, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriasis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.

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

^g Musculoskeletal pain reported during or after discontinuing treatment.

^h Frequency reported as common in paediatric studies.

ⁱ Gravitational oedema, localised oedema, oedema peripheral.

^j Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

^k Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

^l 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, neutropaenia and thrombocytopaenia. 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 adverse reactions, 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 adverse reactions 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 adverse reactions, 6 had 3 adverse reactions, 18 had 4 to 8 adverse reactions 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.

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

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).

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (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 6a.

Table 6a: 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 6b. 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 favourable safety profile.

Table 6b: Selected adverse reactions reported in phase III dose-optimisation study: Advanced phase CML and Ph+ ALL^a

Preferred term	140 mg once daily n = 304	
	All grades	Grade 3/4
	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.

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

Of the 126 Ph+ ALL paediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in these two paediatric studies at a frequency of $\geq 10\%$ in patients on a continuous dosing regimen are shown in Table 7. Of note, pleural effusion was reported in 7 (5.6%) patients in this group, and is therefore not included in the table.

Table 7: Adverse reactions reported in $\geq 10\%$ of paediatric patients with Ph+ ALL treated with SPRYCEL on a continuous dosing regimen in combination with chemotherapy (N=126)^a

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

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

Laboratory test abnormalities

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: neutropaenia (21%), thrombocytopaenia (19%), and anaemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropaenia, thrombocytopaenia, 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, cytopaenias (thrombocytopaenia, neutropaenia, and anaemia) were a consistent finding. However, the occurrence of cytopaenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 8.

Table 8: 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				
Neutropaenia	36	58	77	76
Thrombocytopaenia	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: neutropaenia (Grade 3 $\geq 0.5 - < 1.0 \times 10^9/l$, Grade 4 $< 0.5 \times 10^9/l$); thrombocytopaenia (Grade 3 $\geq 25 - < 50 \times 10^9/l$, Grade 4 $< 25 \times 10^9/l$); anaemia (haemoglobin Grade 3 $\geq 65 - < 80$ g/l, Grade 4 < 65 g/l).

Cumulative grade 3 or 4 cytopaenias among patients treated with 100 mg once daily were similar at 2 and 5 years including: neutropaenia (35% vs. 36%), thrombocytopaenia (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 hypophosphataemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in $\leq 1\%$ 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 hypophosphataemia 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 $\leq 1\%$ 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 hypophosphataemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in $< 1\%$ of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.

Paediatric population

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

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

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

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

Special population

While the safety profile of SPRYCEL in elderly 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 national reporting system listed in Appendix V](#).

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 agents, protein kinase inhibitors, ATC code: L01EA02

Pharmacodynamics

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 PDGF β 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.

Mechanism of action

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, multicentre, 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 9. 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 9: 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 $\leq 0.1\%$ by RQ PCR in peripheral blood samples standardised on the International scale. These are cumulative rates representing minimum follow up for the timeframe specified.

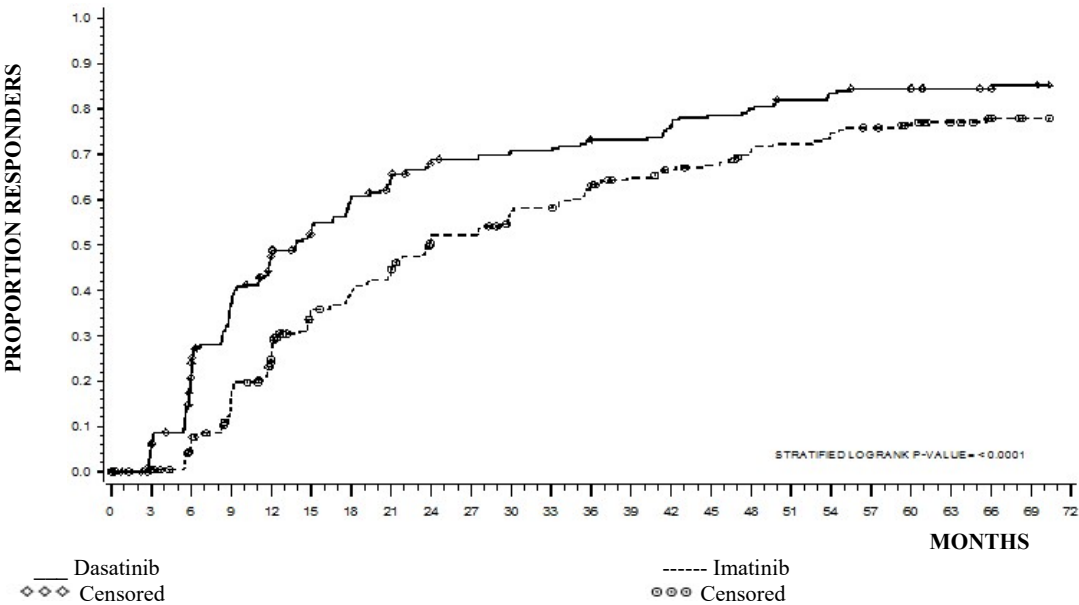
*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.

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)

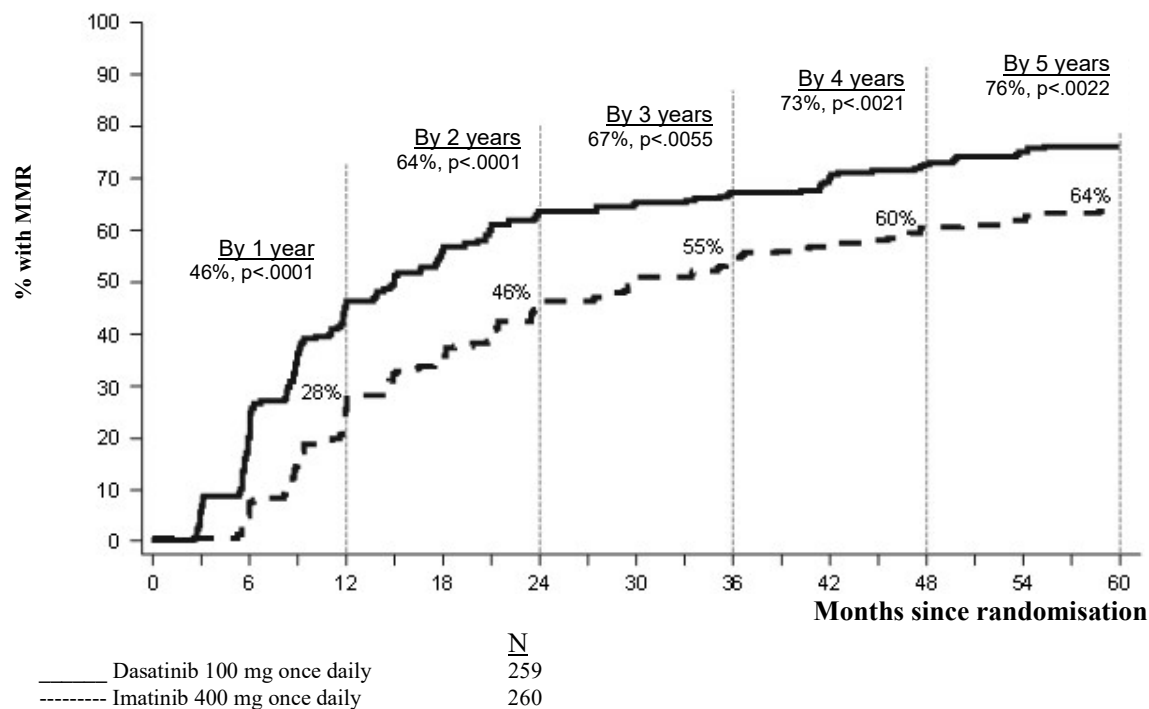


GROUP	# RESPONDERS / # RANDOMIZED	HAZARD RATIO (95% CI)
Dasatinib	198/259	
Imatinib	167/260	
Dasatinib over imatinib		1.54 (1.25 - 1.89)

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 time point are displayed graphically in Figure 2. Rates of MMR were consistently higher in dasatinib-treated patients compared with imatinib-treated patients.

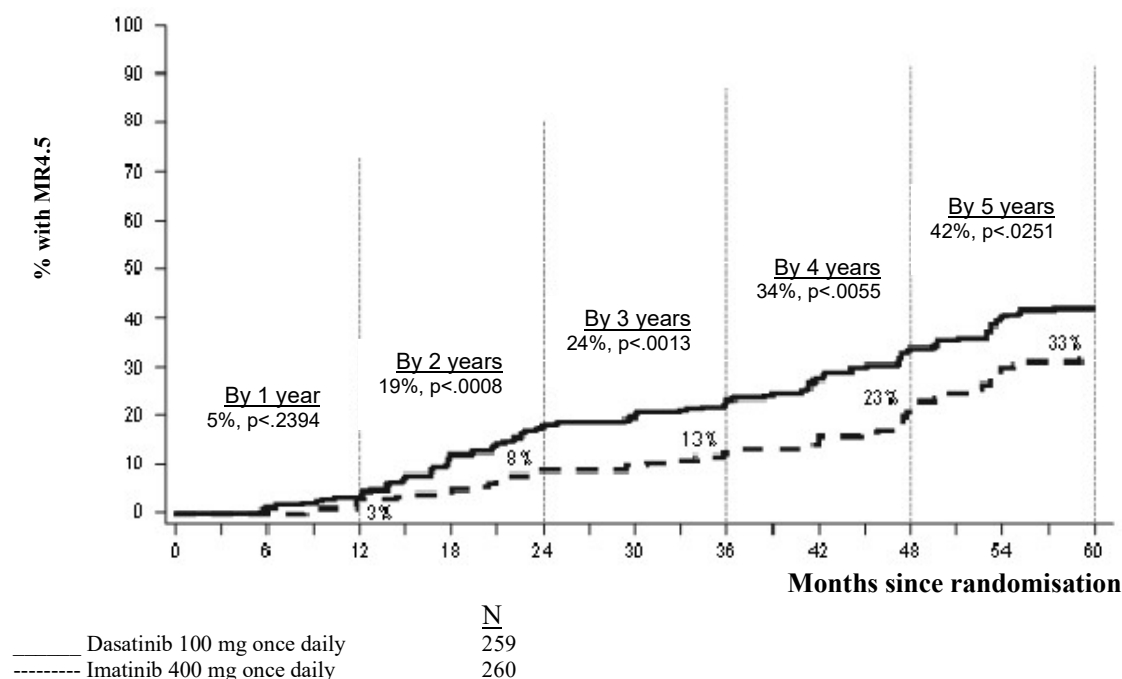
Figure 2: MMR rates over time - all randomised patients in a phase 3 study of newly diagnosed patients with chronic phase CML



The proportion of patients achieving BCR-ABL ratio of $\leq 0.01\%$ (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 $\leq 0.0032\%$ (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 are displayed graphically in Figure 3. Rates of MR4.5 over time were 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).

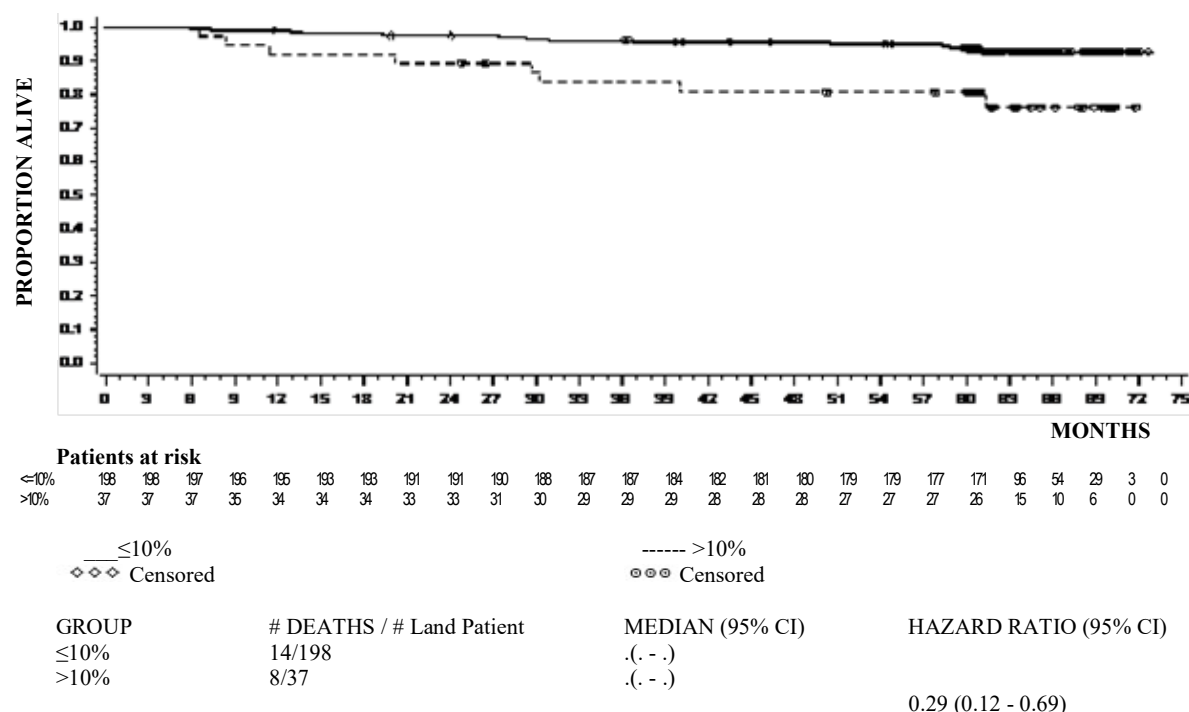
In an additional analysis, more dasatinib-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels $\leq 10\%$ at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free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

Table 10: Dasatinib patients with BCR-ABL $\leq 10\%$ and $> 10\%$ at 3 months

Dasatinib N = 235	Patients with BCR-ABL $\leq 10\%$ 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 time point is displayed graphically in Figure 4. Rate of OS was consistently higher in dasatinib treated patients who achieved BCR-ABL level $\leq 10\%$ at 3 months than those who did not.

Figure 4: Landmark plot for overall survival for dasatinib by BCR-ABL level ($\leq 10\%$ 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).

Study 1

An open-label, randomised, non-comparative multicentre 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 $\leq 0.1\%$ by RQ-PCR in peripheral blood samples) prior to crossover was 29% for dasatinib and 12% for imatinib.

Study 2

An open-label, single-arm, multicentre 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 11. 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, multicentre 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 11.

Myeloid blast phase CML

An open-label, single-arm, multicentre 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 11.

Lymphoid blast phase CML and Ph+ ALL

An open-label, single-arm, multicentre 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 11. 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 11: 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/mm³, 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/mm³, platelets ≥ 100,000/mm³, 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/mm³ and < 1,000/mm³, or platelets ≥ 20,000/mm³ and ≤ 100,000/mm³.

^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.

Study 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 12 and 13.

Table 12: 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
Haematologic response rate^b (%) (95% CI)	
CHR	92% (86–95)
Cytogenetic response^c (%) (95% CI)	
MCyR	
All patients	63% (56–71)
Imatinib-resistant patients	59% (50–68)
CCyR	
All patients	50% (42–58)
Imatinib-resistant patients	44% (35–53)
Major molecular response 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 Haematologic response criteria (all responses confirmed after 4 weeks): Complete haematologic response (CHR) (chronic CML): WBC \leq institutional ULN, platelets $<450,000/\text{mm}^3$, 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 $\leq 0.1\%$ by RQ-PCR in peripheral blood samples

Table 13: 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, $\geq 30\%$ 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%.

Study 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 14.

Table 14: 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	66%	28%	42%	38%
(95% CI)	(59-74)	(18-40)	(26-61)	(23-54)
CHR^b	47%	17%	21%	33%
(95% CI)	(40-56)	(10-28)	(9-39)	(19-49)
NEL^b	19%	11%	21%	5%
(95% CI)	(13-26)	(5-20)	(9-39)	(1-17)
MCyR^c	39%	28%	52%	70%
(95% CI)	(31-47)	(18-40)	(34-69)	(54-83)
CCyR	32%	17%	39%	50%
(95% CI)	(25-40)	(10-28)	(23-58)	(34-66)

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

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

CHR: WBC ≤ institutional ULN, ANC ≥ 1,000/mm³, platelets ≥ 100,000/mm³, 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/mm³ and < 1,000/mm³, or platelets ≥ 20,000/mm³ and ≤ 100,000/mm³.

^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

Paediatric patients with CML

Among 130 patients with chronic phase CML (CML-CP) treated in two paediatric studies, a Phase I, open-label, nonrandomized dose-ranging trial and a Phase II, open-label, nonrandomized trial, 84 patients (exclusively from the Phase II trial) were newly diagnosed with CML-CP and 46 patients (17 from the Phase I trial and 29 from the Phase II trial) were resistant or intolerant to previous treatment with imatinib. Ninety-seven of the 130 paediatric patients with CML-CP were treated with SPRYCEL tablets 60 mg/m² once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Key efficacy endpoints were: complete cytogenetic response (CCyR), major cytogenetic response (MCyR) and major molecular response (MMR). Results are shown in Table 15.

Table 15: Efficacy of SPRYCEL in paediatric patients with CML-CP
Cumulative response over time by minimum follow-up period

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

^a Patients from Phase II paediatric study of newly diagnosed CML-CP receiving oral tablet formulation

^b Patients from Phase I and Phase II paediatric studies of imatinib-resistant or intolerant CML-CP receiving oral tablet formulation

In the Phase I paediatric study, after a minimum of 7 years of follow-up among the 17 patients with imatinib-resistant or intolerant CML-CP, the median duration of PFS was 53.6 months and the rate of OS was 82.4%.

In the Phase II paediatric study, in patients receiving the tablet formulation, estimated 24-month PFS rate among the 51 patients with newly diagnosed CML-CP was 94.0% (82.6, 98.0), and 81.7% (61.4, 92.0) among the 29 patients with imatinib-resistant/intolerant CML-CP. After 24 months of follow-up, OS in newly diagnosed patients was 100%, and 96.6% in imatinib-resistant or intolerant patients. In the Phase II paediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or intolerant patients progressed to blast phase CML.

There were 33 newly diagnosed paediatric patients with CML-CP who received SPRYCEL powder for oral suspension at a dose of 72 mg/m². This dose represents 30% lower exposure compared to the recommended dose (see section 5.2). In these patients, CCyR and MMR were CCyR: 87.9% [95% CI: (71.8-96.6)] and MMR: 45.5% [95% CI: (28.1-63.6)] at 12 months.

Among dasatinib-treated CML-CP paediatric patients previously exposed to imatinib, the mutations detected at the end of treatment were: T315A, E255K and F317L. However, E255K and F317L were also detected prior to treatment. There were no mutations detected in newly diagnosed CML-CP patients at the end of treatment.

Paediatric patients with ALL

The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a pivotal study in paediatric patients over one year of age with newly diagnosed Ph+ ALL.

In this multicenter, historically-controlled Phase II study of dasatinib added to standard chemotherapy, 106 paediatric patients with newly diagnosed Ph+ ALL, of whom 104 patients had confirmed Ph+ ALL, received dasatinib at a daily dose of 60 mg/m² on a continuous dosing regimen for up to 24 months, in combination with chemotherapy. Eighty-two patients received dasatinib tablets exclusively and 24 patients received dasatinib powder for oral suspension at least once, 8 of whom received dasatinib powder for oral suspension exclusively. The backbone chemotherapy regimen was the same as used in the AIEOP-BFM ALL 2000 trial (chemotherapeutic standard multi-agent chemotherapy protocol). The primary efficacy endpoint was 3-year event-free survival (EFS), which was 65.5% (55.5, 73.7).

The minimal residual disease (MRD) negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

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 (AUC_t) 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. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

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

Distribution

In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV% 93%), 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 [¹⁴C]-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

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

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.

Paediatric population

The pharmacokinetics of dasatinib have been evaluated in 104 paediatric patients with leukaemia or solid tumours (72 who received the tablet formulation and 32 who received the powder for oral suspension).

In a paediatric pharmacokinetics study, dose-normalized dasatinib exposure (C_{avg} , C_{min} and C_{max}) appears similar between 21 patients with CP-CML and 16 patients with Ph+ ALL.

A bioequivalence study evaluating the powder for oral suspension to the reference tablet formulation in 77 adult patients showed that the exposure for the powder for oral suspension was 19% less than that of reference tablets. Concentration data in 32 paediatric patients treated with the powder for oral suspension dose of 72 mg/m² was pooled with data from the tablet for a population pharmacokinetic (PPK) analysis, which showed that the exposure of the powder for oral suspension (as measured by time-averaged concentration at steady state [C_{avgss}]) at 72 mg/m² was approximately 30% lower than that of the tablet at 60 mg/m². A PPK model-based simulation predicted that the body weight tiered dosing recommendation described for the powder for oral suspension, in section 4.2 of the Summary of Product Characteristics for the powder for oral suspension, is expected to provide similar exposure to a tablet dose of 60 mg/m². These data should be considered if patients are to switch from powder for oral suspension to tablets or vice versa.

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 embryoletality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryoletality 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

Sucrose

Carmellose sodium

Simethicone emulsion

consisting of:

simeticone,

polyethylene glycol sorbitan tristearate,

polyethoxylate stearate,

glycerides,

methylcellulose,

xanthan gum,

benzoic acid,

sorbic acid,

sulfuric acid.

Tartaric acid

Trisodium citrate anhydrous

Sodium benzoate (E211)

Silica hydrophobic colloidal

Mixed berry flavour [containing benzyl alcohol, sulphur dioxide (E220)]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle

3 years.

After constitution

The oral suspension is stable for 60 days. Store in a refrigerator (2°C - 8°C). Do not freeze.

Constituted oral suspension mixed with milk, yogurt, apple juice, or applesauce may be stored at or below 25°C for up to 1 hour.

6.4 Special precautions for storage

Store below 25°C.

For storage conditions after constitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

120-mL high-density polyethylene bottle with polypropylene child-resistant closure containing 33 g of powder for oral suspension.

Pack size: 1 bottle

Each pack also contains a low-density polyethylene press-in-bottle adapter (PIBA) and a 12-mL oral dosing syringe (polypropylene syringe barrel with high-density polyethylene syringe plunger rod) in a sealed plastic bag.

6.6 Special precautions for disposal and other handling

SPRYCEL powder for oral suspension must be constituted by a pharmacist or qualified healthcare professional prior to being dispensed to the patient. The powder for oral suspension consists of powder blend with the active substance plus excipients, contained within a bottle for constitution. Once constituted, the bottle contains 99 mL of oral suspension, of which 90 mL is intended for dosing and administration.

The use of latex or nitrile gloves is recommended when handling any powder that is inadvertently spilled from the bottle, for appropriate disposal in order to minimise the risk of dermal exposure.

Instructions for constitution of powder for oral suspension

SPRYCEL powder for oral suspension is to be constituted as follows:

Note: If you have to constitute more than one bottle, complete one bottle at a time.

Wash your hands before initiating the constitution. This procedure should be performed on a clean surface.

Step 1: Tap bottom of each bottle (containing 33 g SPRYCEL powder for oral suspension) gently to loosen the powder. Remove child-resistant closure and foil seal. Add 77.0 mL of purified water all at once to the bottle and close tightly with closure.

Step 2: Immediately invert the bottle and shake vigorously for no less than 60 seconds to obtain a uniform suspension. If there are still visible clumps, continue shaking until no clumps are visible. Constitution in this way produces 90 mL (deliverable volume) of 10 mg/mL SPRYCEL oral suspension.

Step 3: Remove the closure, insert the press-in bottle adapter (PIBA) into the bottle neck, and close the bottle tightly with the child-resistant closure.

Step 4: Write the date of expiry of the constituted oral suspension on the bottle label (the date of expiry of the constituted oral suspension is 60 days from the date of constitution).

Step 5: Dispense the bottle with inserted PIBA, package leaflet, and oral dosing syringe in the original carton to the patient or caregiver. Remind the patient or caregiver to shake the bottle vigorously prior to each use.

Instructions for administration to the patient

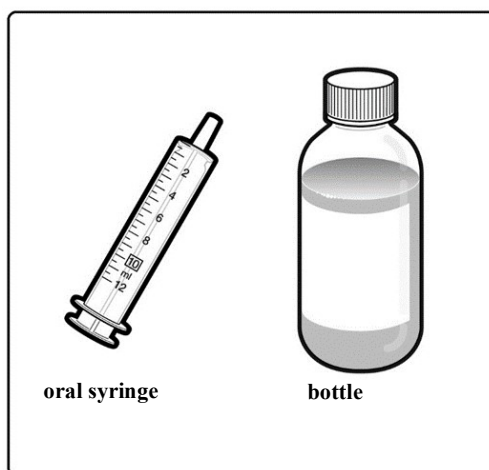
- Take SPRYCEL oral suspension on an empty or full stomach.
- Wash your hands before and after each use.
- Store the constituted oral suspension in a refrigerator (2°C - 8°C). Do not freeze.
- Review total prescribed dose and determine number of milliliters (mL) you will need.
- If the amount needed is greater than 11 mL, it must be split into 2 doses as indicated in Table 16.

Table 16: How to split a dose of oral suspension that is greater than 11 mL

Total prescribed dose (mL)	First dose (mL)	Second dose (mL)
12	6	6
13	7	6
14	7	7
15	8	7
16	8	8

Before you prepare a dose of SPRYCEL oral suspension for administration to the patient, get the following supplies ready:

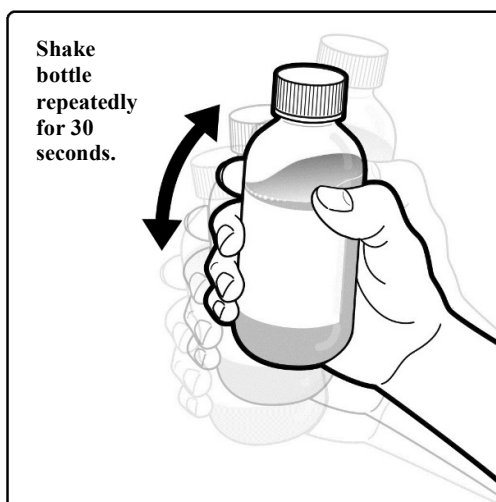
- Paper towel
- 1 SPRYCEL oral suspension bottle containing a white to yellow opaque suspension.
- 12-mL oral syringe provided with the bottle.
- A small container filled with water to use to rinse the syringe.



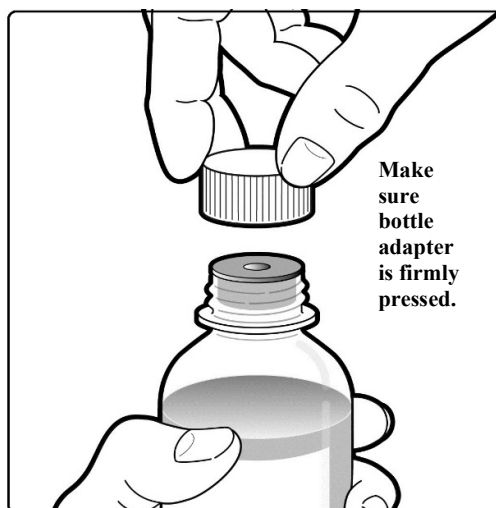
Carefully prepare the SPRYCEL oral suspension for administration, measure the dose, and fill the syringe, like this:

1. Mix the SPRYCEL oral suspension in the closed bottle by shaking for 30 seconds.

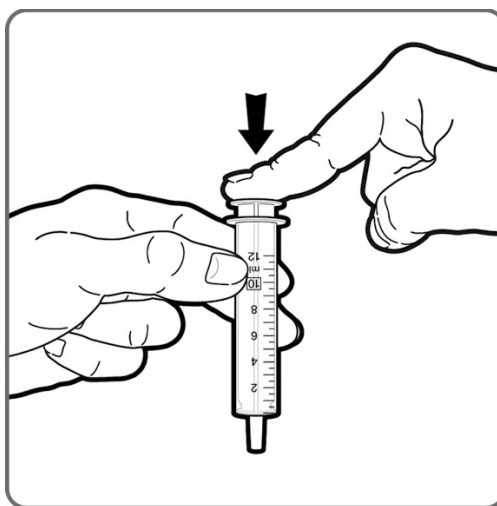
- Shake well before each use.



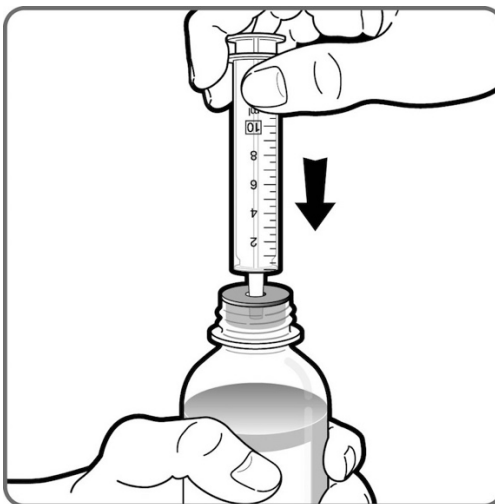
2. Remove the closure from the bottle. Make sure the adapter provided on the bottle for syringe placement is firmly pressed into the bottle.



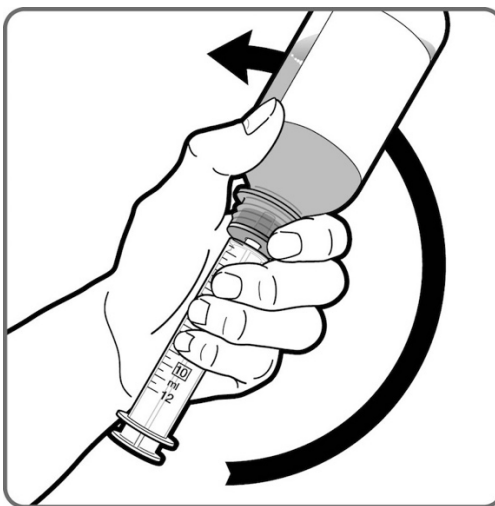
3. Look at the measurements on the side of the syringe so you can see how much to fill it before you begin. Note that the markings on the syringe are in mL. Find the marking that matches the dose that was prescribed by your doctor. Before each use, make sure the syringe plunger is pushed to the bottom of the syringe barrel.



4. With the bottle in an upright position, insert the tip of the syringe firmly into the bottle adapter.

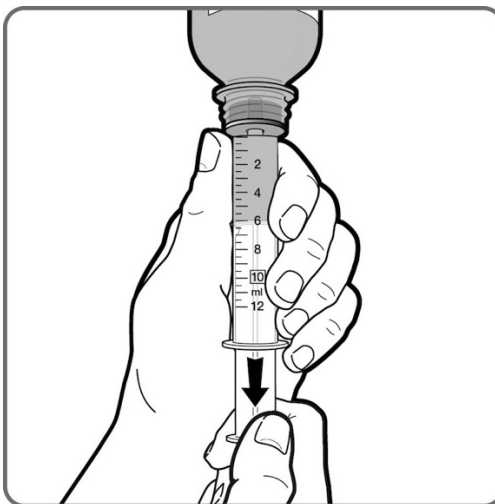


5. Holding the syringe tip firmly into the bottle, turn the bottle with the syringe upside down.

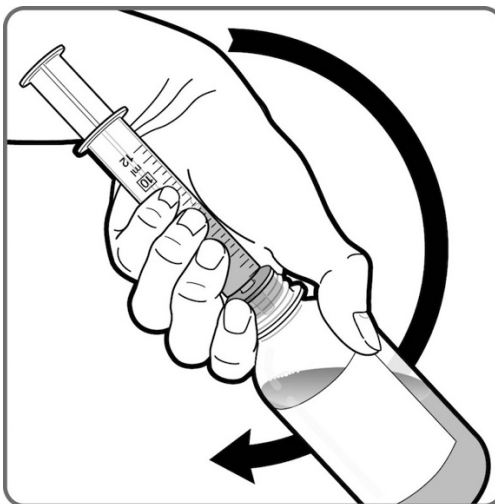


6. Slowly withdraw the amount of SPRYCEL oral suspension prescribed by pulling the syringe plunger until it reaches the marking of the dose prescribed.

- Hold plunger to prevent it from moving. There may be a vacuum pulling the plunger back into barrel.
- If unable to fill with one bottle, use the second bottle to complete the full prescribed dose. Make sure the second bottle is shaken before use.



7. Holding the syringe tip firmly in the bottle, turn the bottle with the syringe upright again.



8. Remove the syringe from the bottle being careful not to depress the plunger.



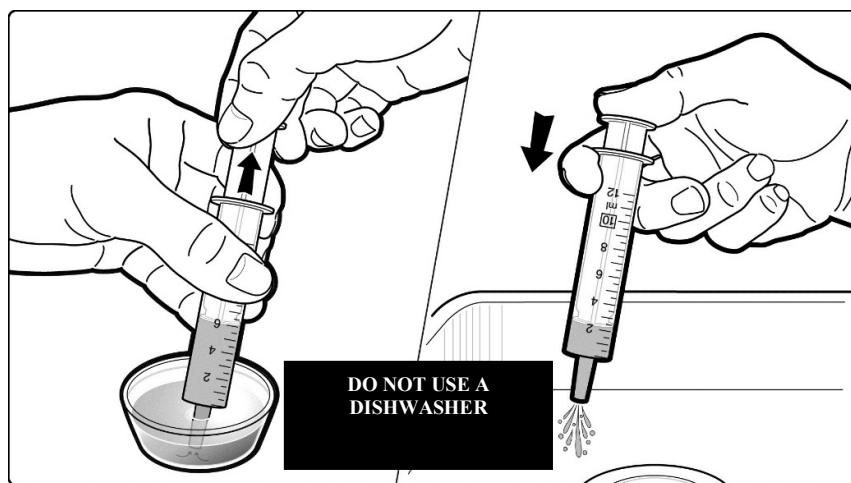
9. With the patient in an upright position, place the tip of the syringe into the mouth between the side of the mouth and the tongue. Slowly push the plunger down until all of the dose has been given.

- Check to make sure the patient has swallowed all of the dose.
- If a second dose is needed to complete the total prescribed dose, repeat steps 3 through 10.
- Put closure back on the bottle and close tightly. Store upright.

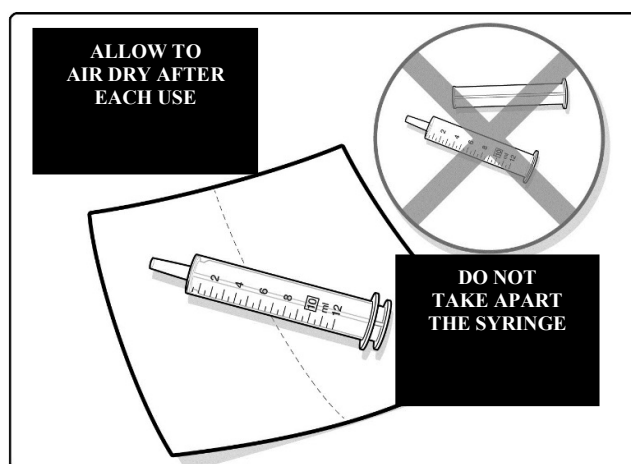


10. Wash the outside and the inside of the syringe with water and allow to air dry after each use to re-use for the next day.

- **Do not wash in a dishwasher.**
- **Do not take the syringe apart in order to avoid damaging it.**



11. Refer to the package leaflet (see section 5 'How to store SPRYCEL') for instructions on discarding any unused medicine, syringe and bottle.



Once constituted, the oral suspension should only be administered using the oral dosing syringe supplied with each pack. Refer to the package leaflet for more detailed instructions for use.

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
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/363/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2006
Date of latest renewal: 15 July 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

SPRYCEL film-coated tablets
Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations,
External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

SPRYCEL 10 mg/mL powder for oral suspension
Swords Laboratories Unlimited Company T/A Lawrence Laboratories
Unit 12 & 15, Distribution Centre
Shannon Industrial Estate
Shannon, Co. Clare, V14 DD39
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

▪ **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

▪ **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency,

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 20 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 x 1 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/004 - 56 film-coated tablets (blisters)
EU/1/06/363/007 - 60 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/001 - 60 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 20 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

calendar pack:

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 50 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 x 1 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/005 - 56 film-coated tablets (blisters)
EU/1/06/363/008 - 60 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/002 - 60 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 50 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

calendar pack:

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 70 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 70 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 x 1 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/006 - 56 film-coated tablets (blisters)
EU/1/06/363/009 - 60 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/003 - 60 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 70 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**BLISTER****1. NAME OF THE MEDICINAL PRODUCT**

SPRYCEL 70 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

calendar pack:

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 80 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/013 - 30 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/012 - 30 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 80 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 100 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/011 - 30 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/010 - 30 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 100 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

**OUTER CARTON AND LABEL FOR BOTTLE PACK
OUTER CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 140 mg film-coated tablets
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/015 - 30 x 1 film-coated tablets (unit dose blisters)
EU/1/06/363/014 - 30 film-coated tablets (bottle)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 140 mg tablets
dasatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL FOR BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

SPRYCEL 10 mg/mL powder for oral suspension
dasatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle of powder for oral suspension contains 990 mg of dasatinib (as monohydrate).
After constitution, one bottle contains 99 mL of oral suspension. Each mL of oral suspension contains 10 mg of dasatinib (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: contains sucrose, sodium, sodium benzoate, benzoic acid, benzyl alcohol and sulphur dioxide (E220).
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
Outer Carton:
1 bottle of 33 g powder
1 bottle adapter
1 oral syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use after constitution.
After constitution, shake bottle well before each use.
Use the oral syringe included in the package.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Powder: Store below 25°C.

After constitution: Store in a refrigerator. Do not freeze. Discard any unused suspension 60 days after constitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/363/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
sprycel 10 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer Carton:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the user

SPRYCEL 20 mg film-coated tablets
SPRYCEL 50 mg film-coated tablets
SPRYCEL 70 mg film-coated tablets
SPRYCEL 80 mg film-coated tablets
SPRYCEL 100 mg film-coated tablets
SPRYCEL 140 mg film-coated tablets
dasatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SPRYCEL is and what it is used for
2. What you need to know before you take SPRYCEL
3. How to take SPRYCEL
4. Possible side effects
5. How to store SPRYCEL
6. Contents of the pack and other information

1. What SPRYCEL is and what it is used for

SPRYCEL contains the active substance dasatinib. This medicine is used to treat chronic myeloid leukaemia (CML) in adults, adolescents and children at least 1 year of age. Leukaemia is a cancer of white blood cells. These white cells usually help the body to fight infection. In people with CML, white cells called granulocytes start growing out of control. SPRYCEL inhibits the growth of these leukaemic cells.

SPRYCEL is also used to treat Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) in adults, adolescents and children at least 1 year of age, and lymphoid blast CML in adults who are not benefiting from prior therapies. In people with ALL, white cells called lymphocytes multiply too quickly and live too long. SPRYCEL inhibits the growth of these leukaemic cells.

If you have any questions about how SPRYCEL works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take SPRYCEL

Do not take SPRYCEL

- if you are **allergic** to dasatinib or any of the other ingredients of this medicine (listed in section 6).

If you could be allergic, ask your doctor for advice.

Warnings and precautions

Talk to your doctor or pharmacist before using SPRYCEL

- if you are taking **medicines to thin the blood** or prevent clots (see "Other medicines and SPRYCEL")

- if you have a liver or heart problem, or used to have one
- if you start **having difficulty breathing, chest pain, or a cough** when taking SPRYCEL: this may be a sign of fluid retention in the lungs or chest (which can be more common in patients aged 65 years and older), or due to changes in the blood vessels supplying the lungs
- if you have ever had or might now have a hepatitis B infection. This is because SPRYCEL could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you experience bruising, bleeding, fever, fatigue and confusion when taking SPRYCEL, contact your doctor. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA).

Your doctor will regularly monitor your condition to check whether SPRYCEL is having the desired effect. You will also have blood tests regularly while you are taking SPRYCEL.

Children and adolescents

Do not give this medicine to children younger than one year of age. There is limited experience with the use of SPRYCEL in this age group. Bone growth and development will be closely monitored in children taking SPRYCEL.

Other medicines and SPRYCEL

Tell your doctor if you are taking, have recently taken or might take any other medicines.

SPRYCEL is mainly handled by the liver. Certain medicines may interfere with the effect of SPRYCEL when taken together.

These medicines are not to be used with SPRYCEL:

- ketoconazole, itraconazole - these are **antifungal medicines**
- erythromycin, clarithromycin, telithromycin - these are **antibiotics**
- ritonavir - this is an **antiviral medicine**
- phenytoin, carbamazepine, phenobarbital - these are treatments for **epilepsy**
- rifampicin - this is a treatment for **tuberculosis**
- famotidine, omeprazole - these are medicines that **block stomach acids**
- St. John's wort - a herbal preparation obtained without a prescription, used to treat **depression** and other conditions (also known as *Hypericum perforatum*)

Do not take medicines that neutralise stomach acids (**antacids** such as aluminium hydroxide or magnesium hydroxide) in the **2 hours before or 2 hours after taking SPRYCEL**.

Tell your doctor if you are taking **medicines to thin the blood** or prevent clots.

SPRYCEL with food and drink

Do not take SPRYCEL with grapefruit or grapefruit juice.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, **tell your doctor immediately**. **SPRYCEL is not to be used during pregnancy** unless clearly necessary. Your doctor will discuss with you the potential risk of taking SPRYCEL during pregnancy.

Both men and women taking SPRYCEL will be advised to use effective contraception during treatment.

If you are breast-feeding, tell your doctor. You should stop breast-feeding while you are taking SPRYCEL.

Driving and using machines

Take special care when driving or using machines in case you experience side effects such as dizziness and blurred vision.

SPRYCEL contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take SPRYCEL

SPRYCEL will only be prescribed to you by a doctor with experience in treating leukaemia. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. SPRYCEL is prescribed for adults and children at least 1 year of age.

The starting dose recommended for adult patients with chronic phase CML is 100 mg once a day.

The starting dose recommended for adult patients with accelerated or blast crisis CML or Ph+ ALL is 140 mg once a day.

Dosing for children with chronic phase CML or Ph+ ALL is on the basis of body weight.

SPRYCEL is administered orally once daily in the form of either SPRYCEL tablets or SPRYCEL powder for oral suspension. SPRYCEL tablets are not recommended for patients weighing less than 10 kg. The powder for oral suspension should be used for patients weighing less than 10 kg and patients who cannot swallow tablets. A change in dose may occur when switching between formulations (i.e., tablets and powder for oral suspension), so you should not switch from one to the other.

Your doctor will decide the right formulation and dose based on your weight, any side effects and response to treatment. The starting dose of SPRYCEL for children is calculated by body weight as shown below:

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

^a The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

There is no dose recommendation for SPRYCEL with children under 1 year of age.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose, or even stopping treatment briefly. For higher or lower doses, you may need to take combinations of the different tablet strengths.

The tablets may come in packs with calendar blisters. These are blisters showing the days of the week. There are arrows to show the next tablet to be taken according to your treatment schedule.

How to take SPRYCEL

Take your tablets at the same time every day. Swallow the tablets whole. **Do not crush, cut or chew them.** Do not take dispersed tablets. You cannot be sure you will receive the correct dose if you crush, cut, chew or disperse the tablets. SPRYCEL tablets can be taken with or without a meal.

Special handling instructions for SPRYCEL

It is unlikely that the SPRYCEL tablets will get broken. But if they do, persons other than the patient should use gloves when handling SPRYCEL.

How long to take SPRYCEL

Take SPRYCEL daily until your doctor tells you to stop. Make sure you take SPRYCEL for as long as it is prescribed.

If you take more SPRYCEL than you should

If you have accidentally taken too many tablets, talk to your doctor **immediately**. You may require medical attention.

If you forget to take SPRYCEL

Do not take a double dose to make up for a forgotten tablet. Take the next scheduled dose at the regular time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following can all be signs of serious side effects:

- if you have chest pain, difficulty breathing, coughing and fainting
- if you experience **unexpected bleeding or bruising** without having an injury
- if you find blood in your vomit, stools or urine, or have black stools
- if you get **signs of infections** such as fever, severe chills
- if you get fever, sore mouth or throat, blistering or peeling of your skin and/or mucous membranes

Contact your doctor immediately if you notice any of the above.

Very common side effects (may affect more than 1 in 10 people)

- **Infections** (including bacterial, viral and fungal)
- **Heart and lungs:** shortness of breath
- **Digestive problems:** diarrhoea, feeling or being sick (nausea, vomiting)
- **Skin, hair, eye, general:** skin rash, fever, swelling around the face, hands and feet, headache, feeling tired or weak, bleeding
- **Pain:** pain in the muscles (during or after discontinuing treatment), tummy (abdominal) pain
- **Tests may show:** low blood platelet count, low white blood cells count (neutropaenia), anaemia, fluid around the lungs

Common side effects (may affect up to 1 in 10 people)

- **Infections:** pneumonia, herpes virus infection (including cytomegalovirus - CMV), upper respiratory tract infection, serious infection of the blood or tissues (including uncommon cases with fatal outcomes)
- **Heart and lungs:** palpitations, irregular heartbeat, congestive heart failure, weak heart muscle, high blood pressure, increased blood pressure in the lungs, cough
- **Digestive problems:** appetite disturbances, taste disturbance, bloated or distended tummy (abdomen), inflammation of the colon, constipation, heartburn, mouth ulceration, weight increase, weight decrease, gastritis
- **Skin, hair, eye, general:** skin tingling, itching, dry skin, acne, inflammation of the skin, persistent noise in ears, hair loss, excessive perspiration, visual disorder (including blurred vision and disturbed vision), dry eye, bruise, depression, insomnia, flushing, dizziness, contusion (bruising), anorexia, somnolence, generalised oedema
- **Pain:** pain in joints, muscular weakness, chest pain, pain around hands and feet, chills, stiffness in muscles and joints, muscle spasm
- **Tests may show:** fluid around the heart, fluid in the lungs, arrhythmia, febrile neutropaenia, gastrointestinal bleeding, high uric acid levels in the blood

Uncommon side effects (may affect up to 1 in 100 people)

- **Heart and lungs:** heart attack (including fatal outcome), inflammation of the lining (fibrous sack) surrounding the heart, irregular heartbeat, chest pain due to lack of blood supply to the

- heart (angina), low blood pressure, narrowing of airway that may cause breathing difficulties, asthma, increased blood pressure in the arteries (blood vessels) of the lungs
- **Digestive problems:** inflammation of the pancreas, peptic ulcer, inflammation of the food pipe, swollen tummy (abdomen), tear in the skin of the anal canal, difficulty in swallowing, inflammation of the gallbladder, blockage of bile ducts, gastro-oesophageal reflux (a condition where acid and other stomach contents come back up into the throat)
 - **Skin, hair, eye, general:** allergic reaction including tender, red lumps on the skin (erythema nodosum), anxiety, confusion, mood swings, lower sexual drive, fainting, tremor, inflammation of the eye which causes redness or pain, a skin disease characterized by tender, red, well-defined blotches with the sudden onset of fever and raised white blood cell count (neutrophilic dermatosis), loss of hearing, sensitivity to light, visual impairment, increased eye tearing, disturbance in skin colour, inflammation of fatty tissue under the skin, skin ulcer, blistering of the skin, nail disorder, hair disorder, hand-foot disorder, renal failure, urinary frequency, breast enlargement in men, menstrual disorder, general weakness and discomfort, low thyroid function, losing balance while walking, osteonecrosis (a disease of reduced blood flow to the bones, which can cause bone loss and bone death), arthritis, skin swelling anywhere in the body
 - **Pain:** inflammation of vein which can cause redness, tenderness and swelling, inflammation of the tendon
 - **Brain:** loss of memory
 - **Tests may show:** abnormal blood test results and possibly impaired kidney function caused by the waste products of the dying tumour (tumour lysis syndrome), low levels of albumin in the blood, low levels of lymphocytes (a type of white blood cell) in the blood, high level of cholesterol in the blood, swollen lymph nodes, bleeding in the brain, irregularity of the electrical activity of the heart, enlarged heart, inflammation of the liver, protein in the urine, raised creatine phosphokinase (an enzyme mainly found in the heart, brain and skeletal muscles), raised troponin (an enzyme mainly found in the heart and skeletal muscles), raised gamma-glutamyltransferase (an enzyme mainly found in the liver), milky-appearing fluid around the lungs (chylothorax)

Rare side effects (may affect up to 1 in 1,000 people)

- **Heart and lungs:** enlargement of the right ventricle in the heart, inflammation of the heart muscle, collection of conditions resulting from blockage of blood supply to the heart muscle (acute coronary syndrome), cardiac arrest (stopping of blood flow from the heart), coronary (heart) artery disease, inflammation of the tissue covering the heart and lungs, blood clots, blood clots in the lungs
- **Digestive problems:** loss of vital nutrients such as protein from your digestive tract, bowel obstruction, anal fistula (an abnormal opening from the anus to the skin around the anus), impairment of kidney function, diabetes
- **Skin, hair, eye, general:** convulsion, inflammation of the optic nerve that may cause a complete or partial loss of vision, blue-purple mottling of the skin, abnormally high thyroid function, inflammation of the thyroid gland, ataxia (a condition associated with lack of muscular coordination), difficulty walking, miscarriage, inflammation of the skin blood vessels, skin fibrosis
- **Brain:** stroke, temporary episode of neurologic dysfunction caused by loss of blood flow, facial nerve paralysis, dementia
- **Immune system:** severe allergic reaction
- **Musculoskeletal and connective tissue:** delayed fusion of the rounded ends that form joints (epiphyses); slower or delayed growth

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

- Inflammation of the lungs
- Bleeding in the stomach or bowels that can cause death
- Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection)
- A reaction with fever, blisters on the skin, and ulceration of the mucous membranes

- Disease of the kidneys with symptoms including oedema and abnormal laboratory test results such as protein in the urine and low protein level in the blood
- Damage to blood vessels known as thrombotic microangiopathy (TMA), including decreased red blood cell count, decreased platelets, and formation of blood clots

Your doctor will check for some of these effects during your treatment.

Reporting of side effects

If you get any side effects, **talk to your doctor or pharmacist**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SPRYCEL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label, blister or carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What SPRYCEL contains

- The active substance is dasatinib. Each film-coated tablet contains 20 mg, 50 mg, 70 mg, 80 mg, 100 mg or 140 mg dasatinib (as monohydrate).
- The other ingredients are:
 - *Tablet core:* lactose monohydrate (see section 2 "SPRYCEL contains lactose"); microcrystalline cellulose; croscarmellose sodium; hydroxypropylcellulose; magnesium stearate
 - *Film-coating:* hypromellose; titanium dioxide (E171); macrogol 400

What SPRYCEL looks like and contents of the pack

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

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

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

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

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

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

SPRYCEL 20 mg, 50 mg or 70 mg film-coated tablets are available in cartons containing 56 film-coated tablets in 4 calendar blisters of 14 film-coated tablets each, and in cartons containing 60 x 1 film-coated tablets in perforated unit dose blisters. They are also available in bottles with child-resistant closure containing 60 film-coated tablets. Each carton contains one bottle.

SPRYCEL 80 mg, 100 mg or 140 mg film-coated tablets are available in cartons containing 30 x 1 film-coated tablets in perforated unit dose blisters. They are also available in bottles with child-resistant closure containing 30 film-coated tablets. Each carton contains one bottle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations,
External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.emea.europa.eu>. There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the user

SPRYCEL 10 mg/mL powder for oral suspension dasatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SPRYCEL is and what it is used for
2. What you need to know before you take SPRYCEL
3. How to take SPRYCEL
4. Possible side effects
5. How to store SPRYCEL
6. Contents of the pack and other information

1. What SPRYCEL is and what it is used for

SPRYCEL contains the active substance dasatinib. This medicine is used to treat chronic myeloid leukaemia (CML) and Philadelphia chromosome positive (Ph⁺) acute lymphoblastic leukaemia (ALL) in adolescents and children from at least one year of age. Leukaemia is a cancer of white blood cells. These white cells usually help the body to fight infection. In people with CML, white cells called granulocytes start growing out of control. SPRYCEL inhibits the growth of these leukaemic cells.

If you have any questions about how SPRYCEL works or why this medicine has been prescribed for you or your child, ask your doctor.

2. What you need to know before you take SPRYCEL

Do not take SPRYCEL

- if **you are allergic** to dasatinib or any of the other ingredients of this medicine (listed in section 6).

If you or your child could be allergic, ask your doctor for advice.

Warnings and precautions

Talk to your doctor or pharmacist before using SPRYCEL

- if you are taking **medicines to thin the blood** or prevent clots (see "Other medicines and SPRYCEL")
- if you have a liver or heart problem, or used to have one
- if you start **having difficulty breathing, chest pain, or a cough** when taking SPRYCEL: this may be a sign of fluid retention in the lungs or chest (which can be more common in patients aged 65 years and older), or due to changes in the blood vessels supplying the lungs
- if you have ever had or might now have a hepatitis B infection. This is because SPRYCEL could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

- if you experience bruising, bleeding, fever, fatigue and confusion when taking SPRYCEL, contact your doctor. This may be a sign of damage to blood vessels known as thrombotic microangiopathy (TMA).

Your doctor will regularly monitor your condition to check whether SPRYCEL is having the desired effect. You or your child will also have blood tests regularly while taking SPRYCEL.

Children and adolescents

Do not give this medicine to children younger than one year of age.

Bone growth and development will be closely monitored in children taking SPRYCEL.

Other medicines and SPRYCEL

Tell your doctor if you are taking, have recently taken or might take any other medicines.

SPRYCEL is mainly handled by the liver. Certain medicines may interfere with the effect of SPRYCEL when taken together.

These medicines are not to be used with SPRYCEL:

- ketoconazole, itraconazole - these are **antifungal medicines**
- erythromycin, clarithromycin, telithromycin - these are **antibiotics**
- ritonavir - this is an **antiviral medicine**
- phenytoin, carbamazepine, phenobarbital - these are treatments for **epilepsy**
- rifampicin - this is a treatment for **tuberculosis**
- famotidine, omeprazole - these are medicines that **block stomach acids**
- St. John's wort - a herbal preparation obtained without a prescription, used to treat **depression** and other conditions (also known as *Hypericum perforatum*)

Do not take medicines that neutralise stomach acids (**antacids** such as aluminium hydroxide or magnesium hydroxide) in the **2 hours before or 2 hours after taking SPRYCEL**.

Tell your doctor if you are taking **medicines to thin the blood** or prevent clots.

SPRYCEL with food and drink

Do not take SPRYCEL with grapefruit or grapefruit juice.

Pregnancy and breast-feeding

If you are pregnant or may be pregnant, **tell your doctor immediately. SPRYCEL is not to be used during pregnancy** unless clearly necessary. Your doctor will discuss with you the potential risk of taking SPRYCEL during pregnancy.

Both men and women taking SPRYCEL will be advised to use effective contraception during treatment.

If you are breast-feeding, tell your doctor. You should stop breast-feeding while you are taking SPRYCEL.

Driving and using machines

Take special care when driving or using machines in case you experience side effects such as dizziness and blurred vision.

SPRYCEL contains sucrose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Contains 0.29 g of sucrose per mL of oral suspension. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth.

SPRYCEL contains sodium

This medicinal product contains 2.1 mg sodium (main component of cooking/table salt) per mL of SPRYCEL oral suspension. At the maximum daily dose of 16 mL oral suspension, this is equivalent to 1.7% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

SPRYCEL contains benzoic acid and sodium benzoate

SPRYCEL contains 0.25 mg benzoic acid in each mL of oral suspension and 0.25 mg sodium benzoate in each mL of oral suspension.

Benzoic acid/Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

SPRYCEL contains benzyl alcohol

SPRYCEL contains 0.017 mg benzyl alcohol in each mL of oral suspension.

Benzyl alcohol may cause allergic reactions.

Use of SPRYCEL is not recommended during pregnancy. Ask your doctor or pharmacist for advice if you are pregnant or breast feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

SPRYCEL contains sulphur dioxide (E220)

May rarely cause severe hypersensitivity reactions and bronchospasm.

3. How to take SPRYCEL

SPRYCEL will only be prescribed by a doctor with experience in treating leukaemia. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

SPRYCEL oral suspension is taken once daily. Your doctor will decide the right dose based on your weight. The starting dose of SPRYCEL is calculated by body weight as shown below:

Body Weight (kg)	Daily Dose, mL (mg)
5 to less than 10 kg	4 mL (40 mg)
10 to less than 20 kg	6 mL (60 mg)
20 to less than 30 kg	9 mL (90 mg)
30 to less than 45 kg	10.5 mL (105 mg)
at least 45 kg	12 mL (120 mg)

SPRYCEL is also available as tablets for use in adults and children from one year of age and weighing more than 10 kg. The powder for oral suspension should be used for patients weighing less than 10 kg and patients who cannot swallow tablets. A change in dose may occur when switching between formulations (i.e., tablets and powder for oral suspension), so you should not switch from one to the other. Your doctor will decide the right formulation and dose based on your weight, any side effects and response to treatment.

There is no dose recommendation for SPRYCEL with children under 1 year of age.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose, or even stopping treatment briefly.

How to take SPRYCEL

Your pharmacist or qualified healthcare professional will constitute (mix to form a liquid) SPRYCEL powder for oral suspension to form SPRYCEL oral suspension before dispensing to you.

SPRYCEL should be taken at the same time every day. SPRYCEL can be taken with or without a meal. SPRYCEL oral suspension may be mixed with milk, yogurt, apple juice, or applesauce.

See the "Instructions for administration to the patient" at the end of the package leaflet for how to give a dose of SPRYCEL oral suspension.

Special handling instructions for SPRYCEL

Persons other than the patient should use gloves when handling SPRYCEL.

Pregnant or breast-feeding women should avoid exposure to SPRYCEL powder for oral suspension.

How long to take SPRYCEL

Take SPRYCEL daily until your doctor tells you to stop. Make sure you take SPRYCEL for as long as it is prescribed.

If you take more SPRYCEL than you should

If you have accidentally taken too much SPRYCEL, talk to your doctor **immediately**. You may require medical attention.

If you forget to take SPRYCEL

Do not take a double dose to make up for a forgotten dose. Take the next scheduled dose at the regular time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following can all be signs of serious side effects:

- if you have chest pain, difficulty breathing, coughing and fainting
- if you experience **unexpected bleeding or bruising** without having an injury
- if you find blood in your vomit, stools or urine, or have black stools
- if you get **signs of infections** such as fever, severe chills
- if you get fever, sore mouth or throat, blistering or peeling of your skin and/or mucous membranes

Contact your doctor immediately if you notice any of the above.

Very common side effects (may affect more than 1 in 10 people)

- **Infections** (including bacterial, viral and fungal)
- **Heart and lungs:** shortness of breath
- **Digestive problems:** diarrhoea, feeling or being sick (nausea, vomiting)
- **Skin, hair, eye, general:** skin rash, fever, swelling around the face, hands and feet, headache, feeling tired or weak, bleeding
- **Pain:** pain in the muscles (during or after discontinuing treatment), tummy (abdominal) pain
- **Tests may show:** low blood platelet count, low white blood cells count (neutropaenia), anaemia, fluid around the lungs

Common side effects (may affect up to 1 in 10 people)

- **Infections:** pneumonia, herpes virus infection (including cytomegalovirus - CMV), upper respiratory tract infection, serious infection of the blood or tissues (including uncommon cases with fatal outcomes)

- **Heart and lungs:** palpitations, irregular heartbeat, congestive heart failure, weak heart muscle, high blood pressure, increased blood pressure in the lungs, cough
- **Digestive problems:** appetite disturbances, taste disturbance, bloated or distended tummy (abdomen), inflammation of the colon, constipation, heartburn, mouth ulceration, weight increase, weight decrease, gastritis
- **Skin, hair, eye, general:** skin tingling, itching, dry skin, acne, inflammation of the skin, persistent noise in ears, hair loss, excessive perspiration, visual disorder (including blurred vision and disturbed vision), dry eye, bruise, depression, insomnia, flushing, dizziness, contusion (bruising), anorexia, somnolence, generalised oedema
- **Pain:** pain in joints, muscular weakness, chest pain, pain around hands and feet, chills, stiffness in muscles and joints, muscle spasm
- **Tests may show:** fluid around the heart, fluid in the lungs, arrhythmia, febrile neutropaenia, gastrointestinal bleeding, high uric acid levels in the blood

Uncommon side effects (may affect up to 1 in 100 people)

- **Heart and lungs:** heart attack (including fatal outcome), inflammation of the lining (fibrous sack) surrounding the heart, irregular heartbeat, chest pain due to lack of blood supply to the heart (angina), low blood pressure, narrowing of airway that may cause breathing difficulties, asthma, increased blood pressure in the arteries (blood vessels) of the lungs
- **Digestive problems:** inflammation of the pancreas, peptic ulcer, inflammation of the food pipe, swollen tummy (abdomen), tear in the skin of the anal canal, difficulty in swallowing, inflammation of the gallbladder, blockage of bile ducts, gastro-oesophageal reflux (a condition where acid and other stomach contents come back up into the throat)
- **Skin, hair, eye, general:** allergic reaction including tender, red lumps on the skin (erythema nodosum), anxiety, confusion, mood swings, lower sexual drive, fainting, tremor, inflammation of the eye which causes redness or pain, a skin disease characterized by tender, red, well-defined blotches with the sudden onset of fever and raised white blood cell count (neutrophilic dermatosis), loss of hearing, sensitivity to light, visual impairment, increased eye tearing, disturbance in skin colour, inflammation of fatty tissue under the skin, skin ulcer, blistering of the skin, nail disorder, hair disorder, hand-foot disorder, renal failure, urinary frequency, breast enlargement in men, menstrual disorder, general weakness and discomfort, low thyroid function, losing balance while walking, osteonecrosis (a disease of reduced blood flow to the bones, which can cause bone loss and bone death), arthritis, skin swelling anywhere in the body
- **Pain:** inflammation of vein which can cause redness, tenderness and swelling, inflammation of the tendon
- **Brain:** loss of memory
- **Tests may show:** abnormal blood test results and possibly impaired kidney function caused by the waste products of the dying tumour (tumour lysis syndrome), low levels of albumin in the blood, low levels of lymphocytes (a type of white blood cell) in the blood, high level of cholesterol in the blood, swollen lymph nodes, bleeding in the brain, irregularity of the electrical activity of the heart, enlarged heart, inflammation of the liver, protein in the urine, raised creatine phosphokinase (an enzyme mainly found in the heart, brain and skeletal muscles), raised troponin (an enzyme mainly found in the heart and skeletal muscles), raised gamma-glutamyltransferase (an enzyme mainly found in the liver), milky-appearing fluid around the lungs (chylothorax)

Rare side effects (may affect up to 1 in 1,000 people)

- **Heart and lungs:** enlargement of the right ventricle in the heart, inflammation of the heart muscle, collection of conditions resulting from blockage of blood supply to the heart muscle (acute coronary syndrome), cardiac arrest (stopping of blood flow from the heart), coronary (heart) artery disease, inflammation of the tissue covering the heart and lungs, blood clots, blood clots in the lungs
- **Digestive problems:** loss of vital nutrients such as protein from your digestive tract, bowel obstruction, anal fistula (an abnormal opening from the anus to the skin around the anus), impairment of kidney function, diabetes

- **Skin, hair, eye, general:** convulsion, inflammation of the optic nerve that may cause a complete or partial loss of vision, blue-purple mottling of the skin, abnormally high thyroid function, inflammation of the thyroid gland, ataxia (a condition associated with lack of muscular coordination), difficulty walking, miscarriage, inflammation of the skin blood vessels, skin fibrosis
- **Brain:** stroke, temporary episode of neurologic dysfunction caused by loss of blood flow, facial nerve paralysis, dementia
- **Immune system:** severe allergic reaction
- **Musculoskeletal and connective tissue:** delayed fusion of the rounded ends that form joints (epiphyses); slower or delayed growth

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

- Inflammation of the lungs
- Bleeding in the stomach or bowels that can cause death
- Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection)
- A reaction with fever, blisters on the skin, and ulceration of the mucous membranes
- Disease of the kidneys with symptoms including oedema and abnormal laboratory test results such as protein in the urine and low protein level in the blood
- Damage to blood vessels known as thrombotic microangiopathy (TMA), including decreased red blood cell count, decreased platelets, and formation of blood clots

Your doctor will check for some of these effects during your treatment.

Reporting of side effects

If you get any side effects, **talk to your doctor or pharmacist**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SPRYCEL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

Powder

Store below 25°C.

After constitution

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard any unused suspension 60 days after constitution.

Constituted oral suspension mixed with milk, yogurt, apple juice, or applesauce may be stored at or below 25°C for up to 1 hour.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What SPRYCEL contains

- The active substance is dasatinib. One bottle of powder for oral suspension contains 990 mg of dasatinib (as monohydrate). After constitution, one bottle contains 99 mL of oral suspension. Each mL of oral suspension contains 10 mg of dasatinib (as monohydrate).
- The other ingredients are: sucrose, carmellose sodium, simethicone emulsion (consisting of simeticone, polyethylene glycol sorbitan tristearate, polyethoxylate stearate, glycerides, methylcellulose, xanthan gum, benzoic acid, sorbic acid, sulfuric acid), tartaric acid, trisodium citrate anhydrous, sodium benzoate (E211), silica hydrophobic colloidal, mixed berry flavour (containing: benzyl alcohol, sulphur dioxide) (see section 2 "What you need to know before you take SPRYCEL").

What SPRYCEL looks like and contents of the pack

SPRYCEL is supplied as a white to off-white powder for oral suspension which forms a white to yellow opaque suspension after constitution with water.

One 120-mL plastic bottle (with child-resistant closure) contains 33 g of powder for oral suspension.

Once constituted, the bottle contains 99 mL of oral suspension, of which 90 mL is intended for dosing and administration.

Each pack also contains a press-in-bottle adapter (PIBA) and a 12-mL oral dosing syringe in a sealed plastic bag.

Each carton contains one bottle.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

Swords Laboratories Unlimited Company T/A Lawrence Laboratories
Unit 12 & 15, Distribution Centre
Shannon Industrial Estate
Shannon, Co. Clare, V14 DD39
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.emea.europa.eu>. There are also links to other websites about rare diseases and treatments.

Instructions for administration to the patient

These instructions show you how to give a dose of SPRYCEL oral suspension to the patient. Once constituted by your pharmacist or healthcare professional, the oral suspension should only be administered using the oral dosing syringe supplied with each pack. Your doctor will decide the right dose based on age and weight. Make sure that you read and understand these instructions before using the oral suspension.

What you need to know before using this medicine

- Take SPRYCEL oral suspension on an empty or full stomach.
- Wash your hands before and after each use.

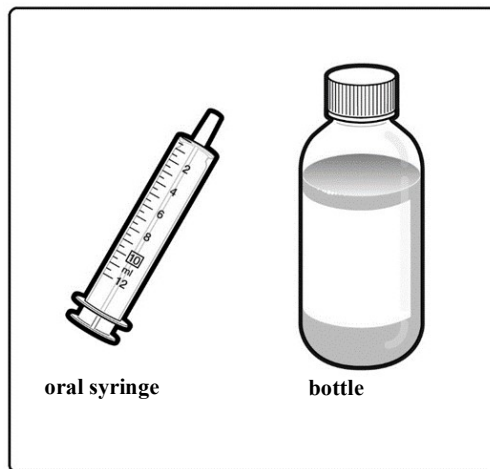
- Store the constituted oral suspension in a refrigerator (2°C - 8°C). Do not freeze.
- Review total prescribed dose and determine number of milliliters (mL) you will need.
- If the amount needed is greater than 11 mL, it must be split into 2 doses as shown below:

How to split a dose that is greater than 11 mL

Total prescribed dose (mL)	First dose (mL)	Second dose (mL)
12	6	6
13	7	6
14	7	7
15	8	7
16	8	8

Before you prepare a dose of SPRYCEL oral suspension for administration to the patient, get the following supplies ready:

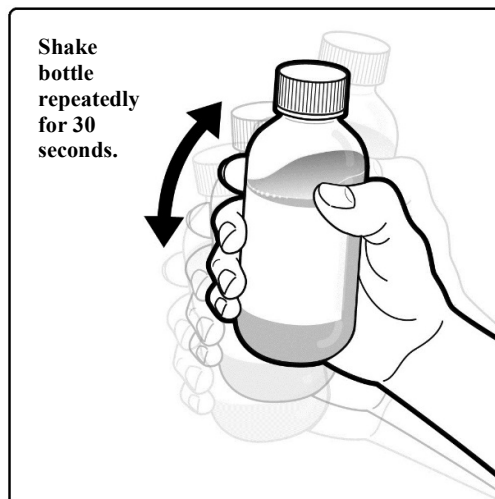
- Paper towel
- 1 SPRYCEL oral suspension bottle containing a white to yellow opaque suspension.
- 12-mL oral syringe provided with the bottle.
- A small container filled with water to use to rinse the syringe.



Carefully prepare the SPRYCEL oral suspension for administration, measure the dose, and fill the syringe, like this:

1. Mix the SPRYCEL oral suspension in the closed bottle by shaking for 30 seconds.

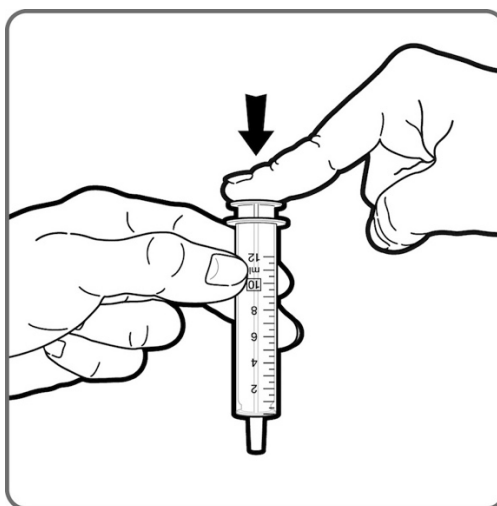
- Shake well before each use.



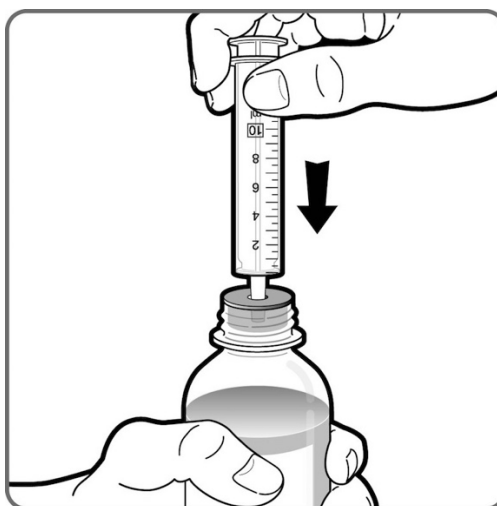
2. Remove the closure from the bottle. Make sure the adapter provided on the bottle for syringe placement is firmly pressed into the bottle.



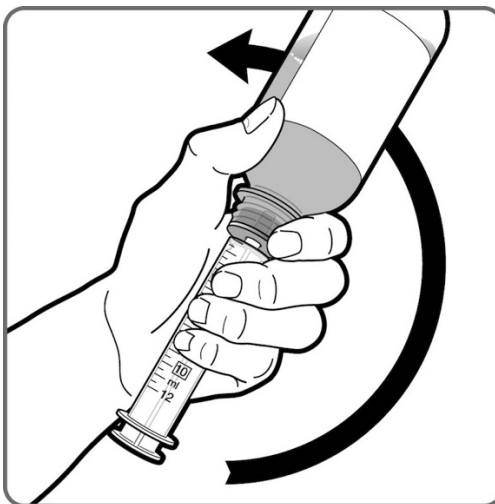
3. Look at the measurements on the side of the syringe so you can see how much to fill it before you begin. Note that the markings on the syringe are in mL. Find the marking that matches the dose that was prescribed by your doctor. Before each use, make sure the syringe plunger is pushed to the bottom of the syringe barrel.



4. With the bottle in an upright position, insert the tip of the syringe firmly into the bottle adapter.

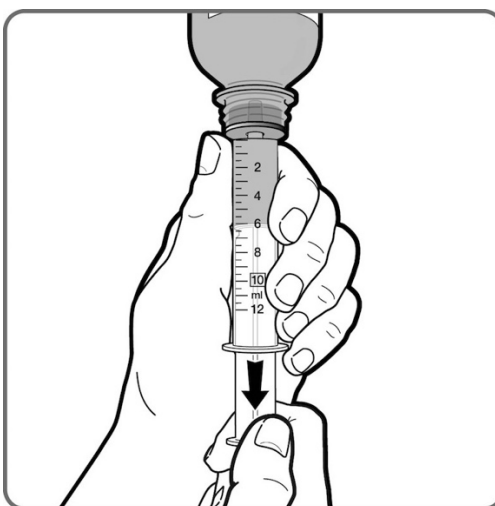


5. Holding the syringe tip firmly into the bottle, turn the bottle with the syringe upside down.

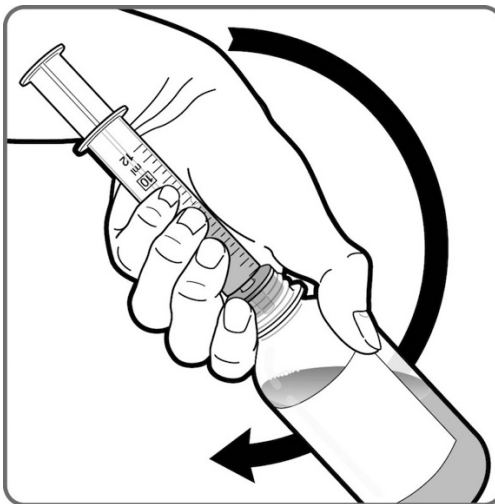


6. Slowly withdraw the amount of SPRYCEL oral suspension prescribed by pulling the syringe plunger until it reaches the marking of the dose prescribed.

- Hold plunger to prevent it from moving. There may be a vacuum pulling the plunger back into barrel.
- If unable to fill with one bottle, use the second bottle to complete the full prescribed dose. Make sure the second bottle is shaken before use.



7. Holding the syringe tip firmly in the bottle, turn the bottle with the syringe upright again.



8. Remove the syringe from the bottle being careful not to depress the plunger.



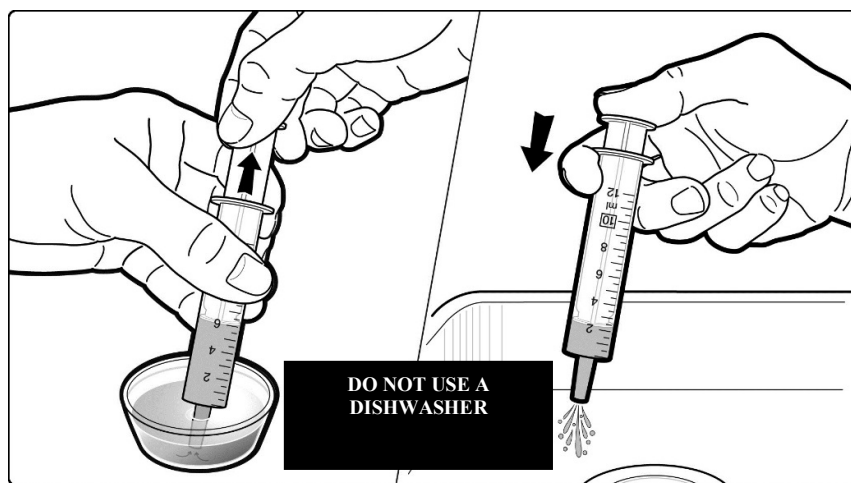
9. With the patient in an upright position, place the tip of the syringe into the mouth between the side of the mouth and the tongue. Slowly push the plunger down until all of the dose has been given.

- Check to make sure the patient has swallowed all of the dose.
- If a second dose is needed to complete the total prescribed dose, repeat steps 3 through 10.
- Put closure back on the bottle and close tightly. Store upright.

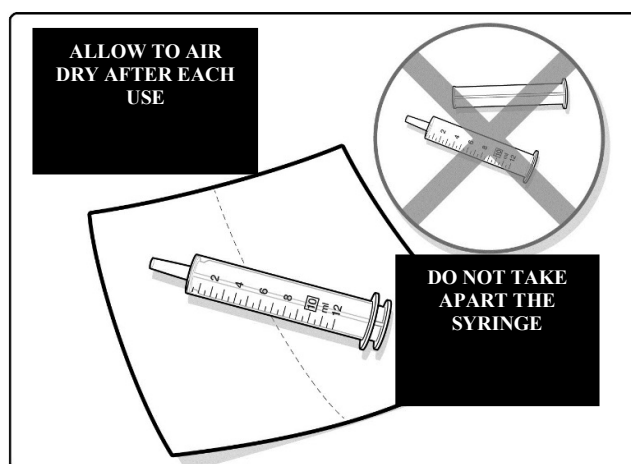


10. Wash the outside and the inside of the syringe with water and allow to air dry after each use to re-use for the next day.

- **Do not wash in a dishwasher.**
- **Do not take the syringe apart in order to avoid damaging it.**



11. Refer to the package leaflet (see section 5 'How to store SPRYCEL') for instructions on discarding any unused medicine, syringe and bottle.



If you have any questions on how to prepare or give a dose of SPRYCEL oral suspension, talk to your doctor, pharmacist or nurse.

The following information is intended for healthcare professionals only:

Instructions for constitution of powder for oral suspension

SPRYCEL powder for oral suspension is to be constituted as follows:

Note: If you have to constitute more than one bottle, complete one bottle at a time.

Wash your hands before initiating the constitution. This procedure should be performed on a clean surface.

Step 1: Tap bottom of each bottle (containing 33 g SPRYCEL powder for oral suspension) gently to loosen the powder. Remove child-resistant closure and foil seal. Add 77.0 mL of purified water all at once to the bottle and close tightly with closure.

Step 2: Immediately invert the bottle and shake vigorously for no less than 60 seconds to obtain a uniform suspension. If there are still visible clumps, continue shaking until no clumps are visible. Constitution in this way produces 90 mL (deliverable volume) of 10 mg/mL SPRYCEL oral suspension.

Step 3: Remove the closure, insert the press-in bottle adapter (PIBA) into the bottle neck, and close the bottle tightly with the child-resistant closure.

Step 4: Write the date of expiry of the constituted oral suspension on the bottle label (the date of expiry of the constituted oral suspension is 60 days from the date of constitution).

Step 5: Dispense the bottle with inserted PIBA, package leaflet, and oral dosing syringe in the original carton to the patient or caregiver. Remind the patient or caregiver to shake the bottle vigorously prior to each use.

ANNEX IV
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE
VARIATION TO THE TERMS OF THE MARKETING
AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for dasatinib, the scientific conclusions of the CHMP are as follows:

In view of available data on chylothorax from clinical trial(s), the literature, spontaneous reports including in 13 cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between dasatinib and chylothorax is at least a reasonable possibility. The PRAC concluded that the product information of products containing dasatinib should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for dasatinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dasatinib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.