SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SPRYCEL® 20 mg tablets (dasatinib)

SPRYCEL® 50 mg tablets (dasatinib)

SPRYCEL® 70 mg tablets (dasatinib)

SPRYCEL® 100 mg tablets (dasatinib)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SPRYCEL tablets are available for oral administration in strengths of 20 mg, 50 mg, 70 mg and 100 mg of dasatinib.

Contains sugar (lactose).

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

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

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

SPRYCEL 50 mg tablets are available as white to off-white, oval, biconvex, film-coated tablets with "BMS" debossed on one side and "528" on the other side.

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

SPRYCEL 100 mg tablets are available as white to off-white, oval, biconvex, film-coated tablets with "BMS

100" debossed on one side and "852" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPRYCEL is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase.

SPRYCEL is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) with resistance or intolerance to prior therapy.

4.2 Posology and method of administration

Posology

The recommended starting dosage of SPRYCEL for chronic phase CML is 100 mg administered orally once daily.

The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML or Ph+ ALL is 70 mg twice daily, administered orally.

Dose increase or reduction is recommended based on individual patient response and tolerability.

Dose escalation:

In clinical trials of CML and Ph+ ALL, dose escalation to a total maximum of 70 mg twice-daily (chronic phase CML) or 90 mg twice daily (advanced phase CML or Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage.

Dose adjustment for undesirable effects:

Myelosuppression:

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

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 100 mg once daily)	ANC* < 0,5 × 10^9/l or Platelets < 50 × 10^9/l	1. Stop SPRYCEL until ANC ≥ 1,0 × 10^9/l and platelets ≥ 50 × 10^9/l. 2. Resume treatment with SPRYCEL at the original starting dose. 3. If platelets < 25 × 10^9/l or recurrence of ANC < 0,5 × 10^9/l for > 7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib).

Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg twice daily)	ANC < 0,5 × 10^9/l or Platelets < 10 × 10^9/l	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop SPRYCEL until ANC ≥ 1,0 × 10^9/l and platelets ≥ 20 × 10^9/l and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). 4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily.

*ANC: absolute neutrophil count

Non-haematological adverse reactions:

If a moderate (Grade 2) non-hematologic adverse reaction develops with SPRYCEL, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe (Grade 3 or 4) non-haematological adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event.

For adult patients with chronic phase CML who received 100 mg once daily, dose reduction to 80 mg once daily with further reduction from 80 mg once daily to 50 mg once daily, if needed, is recommended. For adult patients with advanced phase CML or Ph+ ALL who received 140 mg once daily, dose reduction to 100 mg once daily with further reduction from 100 mg once daily to 80mg once daily, if needed, is recommended (see section 4.4).

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** ***Effect of other medicines on SPRYCEL***). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

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

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

Duration of treatment

In clinical studies, treatment with SPRYCEL in adults with chronic phase CML; accelerated, myeloid or lymphoid blast phase (advanced phase) CML; or Ph+ ALL was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response [CCyR]) or major molecular response (MMR and MR4.5) has not been investigated.

Special populations

Renal Impairment:

(See section **5.2 Pharmacokinetic properties**, Special populations).

Hepatic Impairment:

Cases of hepatic failure including fatal outcome have occurred in patients treated with SPRYCEL (see Undesirable Effects). Only 1 case of hepatic failure reported, but no fatalities due to hepatic failure and no cases of hepatitis B reactivation out of 5 458 patients in the clinical trial database. (See section 5.2 **Pharmacokinetic properties, Special populations**).

Geriatric: No clinically relevant age-related pharmacokinetic differences have been observed. No specific dose recommendation is necessary in the elderly.

Paediatric population

The safety and efficacy of SPRYCEL in patients < 18 years of age have not been established.

Method of administration

Tablets should not be crushed, cut or chewed; they should be swallowed whole to maintain dosing

consistency and minimize the risk of dermal exposure. Film-coated tablets should not be dispersed, as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet.

SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

SPRYCEL should not be taken with grapefruit or grapefruit juice (see **4.5 Medicine that may increase dasatinib plasma concentrations**).

4.3 Contraindications

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

The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended.

4.4 Special warnings and precautions for use

Myelosuppression

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

In adult patients with advanced phase CML or Ph+ ALL treated with dasatinib as monotherapy, complete blood counts (CBCs) should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated.

In adult patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily or by dose reduction (see section 4.2 and section 4.8).

Bleeding related events

In patients with chronic phase CML, severe haemorrhage occurred in 5 patients receiving SPRYCEL at the

recommended dose (n=548).

In patients with advanced phase CML or Ph+ ALL, severe (Grade 3 or 4) central nervous system (CNS) haemorrhage, including fatalities, occurred in 1 % of patients receiving SPRYCEL at the recommended dose (n=304). Severe gastrointestinal haemorrhage, including fatalities, occurred in 6 % of patients and generally required treatment interruptions and transfusions. Other cases of severe haemorrhage occurred in 2 % of patients.

Most bleeding events in clinical studies were associated with severe thrombocytopenia.

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

SPRYCEL is associated with fluid retention. After 5 years of follow-up in the Phase III newly diagnosed chronic phase CML study (n=258), severe fluid retention was reported in 13 patients (5 %) receiving SPRYCEL.

In all patients with newly diagnosed or imatinib resistant or intolerant patients with chronic phase CML (n=548), severe fluid retention occurred in 32 (6 %) patients receiving SPRYCEL at the recommended dose.

In patients with advanced phase CML or Ph+ ALL receiving SPRYCEL, severe fluid retention was reported in 8 % of patients, including severe pleural and pericardial effusion reported in 7 % and 1 % of patients, respectively. In these patients, severe pulmonary oedema and severe pulmonary hypertension were reported in 1 % of patients.

Patients who develop symptoms suggestive of pleural effusion or other fluid retention, such as new or worsened dyspnoea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with chest X-ray or additional diagnostic imaging as appropriate. Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids (see section 4.2).

While the safety profile of SPRYCEL in the elderly population was similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention events and dyspnoea and should be monitored closely. Cases of chylothorax have also been reported in patients presenting with pleural effusion (see section 4.8).

Cardiac Adverse Reactions

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

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in SPRYCEL

1. Cerebrovascular adverse events

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g., cerebrovascular accident, transient ischaemic attack, ischaemic stroke and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with SPRYCEL should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events. Treatment with SPRYCEL should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

2. Hepatic failure and hepatitis B virus reactivation

BCR-ABL TKIs, including SPRYCEL have been associated with hepatitis B virus (HBV) reactivation including acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Screening for HBV should be considered in accordance with guidelines before starting therapy with SPRYCEL. Consultation with a medical practitioner with expertise in the treatment of HBV is recommended for patients who test positive for HBV serology.

Patients who are carriers of HBV and require treatment with SPRYCEL should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop reactivation of HBV while receiving SPRYCEL, prompt consultation with a medical practitioner with expertise in the treatment of HBV is recommended.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterisation, has been reported in association with SPRYCEL treatment. In these cases, PAH was reported after initiation of SPRYCEL therapy, and also after more than one year of treatment. Patients with PAH reported during SPRYCEL treatment were often taking concomitant medications or had co-morbidities in addition to the underlying malignancy.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL therapy. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for more common aetiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. During this evaluation, guidelines for non-haematologic adverse reactions should be followed (see section 4.2). If the adverse reaction is severe, treatment must be withheld until the event has resolved or improved. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, SPRYCEL should be permanently discontinued. Follow-up should be performed according to standard practice guidelines. Improvements in haemodynamic and clinical parameters have been observed

in SPRYCEL-treated patients with PAH following cessation of SPRYCEL therapy.

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT interval).

After 5 years of follow-up in the Phase III clinical study of newly diagnosed chronic phase CML, 1 patient (< 1 %) in each of the SPRYCEL (n=258) and imatinib (n=258) treatment groups had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3,0 msec in SPRYCEL-treated patients. One patient (< 1 %) experienced QTcF > 500 msec.

In 865 patients with leukaemia treated with SPRYCEL in Phase II clinical studies, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 – 6 msec; the upper 95 % confidence intervals for all mean changes from baseline were < 7 msec. Of the 2 182 patients with resistance or intolerance to prior imatinib therapy treated with SPRYCEL in clinical studies, 15 (1 %) had QT prolongation reported as an adverse reaction. Twenty-one of these patients (1 %) experienced a QTcF > 500 msec.

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

Severe dermatologic reactions

Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, have been reported with the use of SPRYCEL. SPRYCEL should be permanently discontinued in patients who experience a severe mucocutaneous reaction during

treatment if no other aetiology can be identified.

Geriatric use

Patients aged 65 years and older are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance, and are more likely to experience the less frequently reported events of abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease, and should be monitored closely.

Lactose

SPRYCEL contains 135 mg of lactose monohydrate in a 100 mg daily dose and 189 mg of lactose monohydrate in a 140 mg daily dose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SPRYCEL.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on SPRYCEL:

Medicines that may increase dasatinib plasma concentrations:

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of SPRYCEL and medicines that inhibit CYP3A4 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin, grapefruit juice) may increase exposure to dasatinib and should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity (see section **4.2 Dose reduction for concomitant use of strong CYP3A4 inhibitors)**.

Medicines that may decrease dasatinib plasma concentrations:

CYP3A4 Inducers: Medicines that induce CYP3A4 activity (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort (*Hypericum perforatum)*), may reduce exposure to dasatinib. Concomitant use of potent CYP3A4 inducers with SPRYCEL is not recommended. In patients for whom CYP3A4 inducers are indicated, alternative agents with no or minimal CYP3A4 induction potential should be selected.

Rifampicin: Data from a study of 20 healthy subjects indicate that when a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampicin, a potent CYP3A4 inducer, the mean C_{max} and AUC of dasatinib were decreased by 81 % and 82 %, respectively.

Antacids (aluminium hydroxide/magnesium hydroxide products): Non-clinical data demonstrate that the solubility of dasatinib is pH dependent. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Simultaneous administration of SPRYCEL with antacids should be avoided.

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors reduces dasatinib exposure by > 60 %. The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

Effect of SPRYCEL on other medicines:

CYP3A4 Substrates: Dasatinib is an inhibitor of CYP3A4. Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, cisapride, ciclosporin, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

Simvastatin: Single dose data from a study of 54 healthy subjects indicate that the mean C_{max} and AUC of

simvastatin, a CYP3A4 substrate, were increased by 37 % and 20 %, respectively, when simvastatin was administered in combination with a single 100 mg dose of SPRYCEL.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Sexually active male or female patients taking SPRYCEL should use adequate contraception.

Pregnancy

Dasatinib may cause foetal harm when administered to a pregnant woman.

There have been post-marketing reports of spontaneous abortion and foetal and infant anomalies from women who have taken SPRYCEL during pregnancy.

SPRYCEL is not recommended for use in women who are pregnant or contemplating pregnancy. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

Women who are taking SPRYCEL should not breastfeed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The data described below reflect exposure to SPRYCEL in 324 patients with newly diagnosed chronic phase CML and in 2 388 patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+

ALL.

In the Phase III newly diagnosed chronic phase CML study, the median duration of therapy was approximately 60 months (range 0,03 – 72,7 months) for SPRYCEL. The median duration of therapy in 1 618 patients with chronic phase CML was 29 months (range 0 – 92,9 months). In 1094 patients with advanced phase CML or Ph+ ALL, the median duration of treatment for patients was 6,2 months (range 0 – 93,2 months).

In the overall population of 2 712 SPRYCEL-treated subjects, 520 (19 %) experienced adverse reactions leading to treatment discontinuation.

In the Phase III newly diagnosed chronic phase CML study, treatment was discontinued for adverse reactions in 14 % of patients receiving SPRYCEL with a minimum of 60 months follow-up. Among the 1 618 SPRYCEL-treated subjects with chronic phase CML, adverse reactions leading to discontinuation were reported in 329 (20,3 %) subjects, and among the 1 094 SPRYCEL-treated subjects with advanced phase disease, adverse reactions leading to discontinuation were reported in 191 (17,5 %) subjects.

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

Adverse reactions reported in multiple clinical studies of SPRYCEL that were considered at least possibly related to SPRYCEL are listed by system organ class and frequency. The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000). These events are included based on clinical relevance.

Infections and infestations	
Very common:	infection (including bacterial, viral, fungal, non-specified)
Common:	pneumonia (including bacterial, viral and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon reports of fatal outcomes)
Blood and lymphatic system disorders	
Very common:	myelosuppression (including anaemia, neutropenia, thrombocytopenia)
Common:	febrile neutropenia
Uncommon:	lymphadenopathy, lymphopenia
Rare:	pure red cell aplasia
Immune system disorders	
Uncommon:	hypersensitivity (including erythema nodosum)
Endocrine disorders	
Uncommon:	hypothyroidism
Rare:	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
Common:	appetite disturbances[a], hyperuricaemia
Uncommon:	tumour lysis syndrome, dehydration, hypoalbuminaemia, hypercholesterolaemia
Rare:	diabetes mellitus
Psychiatric disorders	
Common:	depression, insomnia
Uncommon:	anxiety, confusional state, affect lability, decrease of libido
Nervous system disorders	
Very common:	headache

Common:	dizziness, neuropathy (including peripheral neuropathy), dysgeusia, somnolence
Uncommon:	CNS bleeding [b], amnesia, tremor, syncope, balance disorder
Rare:	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
Common:	visual disorder (including visual disturbance, blurred vision and reduced visual acuity), dry eye
Uncommon:	visual impairment, conjunctivitis, photophobia, increased lacrimation
Ear and labyrinth disorders	
Common:	tinnitus
Uncommon:	hearing loss, vertigo
Cardiac disorders	
Common:	congestive heart failure/cardiac dysfunction[c], pericardial effusion, dysrhythmia (including tachycardia), palpitations
Uncommon:	cardiomegaly, angina pectoris, myocardial infarction (including fatal outcomes), electrocardiogram QT prolonged, pericarditis, ventricular dysrhythmia (including ventricular tachycardia), electrocardiogram T wave abnormal, increased troponin
Rare:	acute coronary syndrome, myocarditis, cor pulmonale, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Vascular disorders	
Very common:	haemorrhage [d]
Common:	hypertension, flushing
Uncommon:	hypotension, thrombophlebitis, thrombosis

Rare:	deep vein thrombosis, pulmonary embolism, livedo reticularis
Respiratory, thoracic and mediastinal disorders	
Very common:	pleural effusion, dyspnoea
Common:	pulmonary oedema, pulmonary hypertension, lung infiltration, pneumonitis, cough
Uncommon:	pulmonary arterial hypertension, bronchospasm, asthma, dysphonia, chylothorax*
Rare:	pulmonary embolism, acute respiratory distress syndrome
Gastrointestinal disorders	
Very common:	diarrhoea, nausea, vomiting, abdominal pain
Common:	gastrointestinal bleeding, abdominal distension, mucosal inflammation (including mucositis/stomatitis), colitis (including neutropenic colitis), gastritis, oral soft tissue disorder, dyspepsia, constipation
Uncommon:	pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastro-oesophageal reflux disease
Rare:	protein-losing gastroenteropathy, ileus, acute pancreatitis, anal fistula
Hepatobiliary disorders	
Uncommon:	hepatitis, cholestasis, cholecystitis
Skin and subcutaneous tissue disorders	
Very common:	skin rash[e]
Common:	pruritus, alopecia, acne, dry skin, urticaria, hyperhidrosis, dermatitis (including eczema)
Uncommon:	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodys[~~a~~]esthesia syndrome, hair disorder

Rare:	leukocytoclastic vasculitis, skin fibrosis
Musculoskeletal and connective tissue disorders	
Very common:	musculoskeletal pain
Common:	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Uncommon:	rhabdomyolysis, osteonecrosis, tendonitis, muscle inflammation, arthritis
Renal and urinary disorders	
Uncommon:	renal failure, urinary frequency, proteinuria
Rare	renal impairment
Pregnancy, puerperium and perinatal condition	
Rare:	abortion
Reproductive system and breast disorders	
Uncommon:	gynaecomastia, menstrual disorder
General disorders and administration site conditions	
Very common:	peripheral oedema[g], fatigue, pyrexia, face oedema[h]
Common:	asthenia, pain, chest pain, generalised oedema[h], chills
Uncommon:	malaise, other superficial oedema[i],
Rare:	gait disturbance
Investigations	
Common:	decreased weight, increased weight
Uncommon:	increased blood creatinine phosphokinase, increased gamma-glutamyltransferase
Injury, poisoning, and procedural complications	
Common:	contusion

Adverse reactions (excluding laboratory abnormalities), that were reported in at least 10 % of patients with

Ph+ ALL and CML resistant or intolerant to prior imatinib therapy are shown in **Table 2** below.

Table 2: Adverse Reactions Reported in ≥ 10 % of Patients with Ph+ ALL and CML Resistant or Intolerant to Prior Imatinib Therapy

1. 2.		**100 mg Once daily**		**70 mg Twice Daily**							
3. 4.		**Chronic (n=165)**		**Accelerated (n=345)**		**Myeloid Blast (n=206)**		**Lymphoid Blast (n=82)**		**Ph+ALL (n=95)**	
5. 6.	**Preferred Term**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
7.		**Percent (%) of Patients**									
8. 9.	Fluid Retention	34	4	53	10	48	17	37	6	39	11
10. 11. 12.	Superficial localised oedema	18	0	28	1	24	1	24	0	19	1
13. 14.	Pleural effusion	18	2	37	6	32	13	22	5	27	9
15. 16.	Generalised oedema	3	0	6	1	5	<1	1	0	6	2
17. 18.	Pericardial effusion	2	1	8	2	8	3	5	0	3	0
19. 20. 21. 22. 23.	Congestive heart failure/cardiac dysfunction[c]	0	0	3	1	3	2	1	1	1	1
24. 25.	Pulmonary oedema	0	0	3	1	1	<1	2	1	4	1
26.	Headache	33	1	27	1	10	1	20	4	11	1
27.	Diarrhoea	27	2	42	5	31	5	34	4	29	6
28.	Fatigue	24	2	23	4	14	1	21	5	12	0

1. 2.		**100 mg Once daily**		**70 mg Twice Daily**							
3. 4.		**Chronic (n=165)**		**Accelerated (n=345)**		**Myeloid Blast (n=206)**		**Lymphoid Blast (n=82)**		**Ph+ALL (n=95)**	
5. 6.	**Preferred Term**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
7.		**Percent (%) of Patients**									
29.	Dyspnoea	20	2	26	6	18	6	13	1	18	2
30. 31.	Musculo-skeletal pain	19	2	18	1	11	<1	10	0	5	1
32.	Nausea	18	1	22	1	17	2	23	1	23	2
33.	Skin rash[e]	17	2	25	1	18	<1	16	2	21	1
34.	Myalgia	13	0	12	1	3	0	5	0	4	0
35.	Arthralgia	12	1	12	1	6	1	5	0	2	0
36. 37. 38. 39. 40. 41.	Infection (including bacterial, viral, fungal, and non-specified)	12	1	12	3	7	4	6	1	7	4
42. 43.	Abdominal pain	12	1	11	<1	9	1	11	1	7	2
44.	Haemorrhage	11	1	36	12	34	14	17	5	21	11
45. 46. 47.	Gastrointestinal bleeding	2	1	17	9	17	10	2	1	13	8
48. 49.	CNS bleeding	0	0	2	<1	1	<1	4	2	2	1
50.	Vomiting	7	1	18	2	16	1	20	4	15	1
51.	Cough	6	0	12	1	10	<1	9	0	5	0
52.	Pyrexia	5	1	19	3	16	2	16	1	18	1

1. 2.		**100 mg Once daily**		**70 mg Twice Daily**							
3. 4.		**Chronic (n=165)**		**Accelerated (n=345)**		**Myeloid Blast (n=206)**		**Lymphoid Blast (n=82)**		**Ph+ALL (n=95)**	
5. 6.	**Preferred Term**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
7.		**Percent (%) of Patients**									
53. 54. 55. 56. 57.	Mucosal Inflammation (including mucositis/ stomatitis)	5	0	12	<1	8	<1	4	0	3	1
58.	Asthenia	5	0	11	2	7	1	6	1	11	4
59.	Anorexia	4	0	13	<1	10	<1	6	0	9	0
60. 61.	Febrile neutropenia	1	1	10	9	6	6	13	12	7	7

a Includes decreased appetite, early satiety, increased appetite.

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

c Includes increased brain natriuretic peptide, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, decreased ejection fraction, ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesi.

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

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

f Includes gravitational oedema, localised oedema, peripheral oedema.

g Includes conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, mouth oedema, orbital oedema, periorbital oedema, face swelling.

h Includes fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

i Includes genital swelling, incision site oedema, genital oedema, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

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

Laboratory Findings

Table 3 shows laboratory findings from a clinical trial in patients with newly diagnosed chronic phase CML. There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.

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

	SPRYCEL (n = 258)
	Percent (%) of Patients
Haematology Parameters	
Neutropenia	29
Thrombocytopenia	22
Anaemia	13
Biochemistry Parameters	

Hypophosphataemia	7
Hypokalaemia	0
Hypocalcaemia	4
Elevated SGPT (ALT)	<1
Elevated SGOT (AST)	<1
Elevated Bilirubin	1
Elevated Creatinine	1

CTC grades: neutropenia (Grade 3 ≥ 0,5 – < 1,0 × 10^9/l, Grade 4 < 0,5 × 10^9/l); thrombocytopenia (Grade 3 ≥ 25 – < 50 × 10^9/l, Grade 4 < 25 × 10^9/l); anaemia (haemoglobin Grade 3 ≥ 65 – < 80 g/l, Grade 4 < 65 g/l); elevated creatinine (Grade 3 > 3 – 6 × upper limit of normal range (ULN), Grade 4 > 6 × ULN); elevated bilirubin (Grade 3 > 3 – 10 × ULN, Grade 4 > 10 × ULN); elevated SGOT or SGPT (Grade 3 > 5 – 20 × ULN, Grade 4 > 20 × ULN); hypocalcaemia (Grade 3 < 7,0 – 6,0 mg/dl, Grade 4 < 6,0 mg/dl); hypophosphataemia (Grade 3 < 2,0 – 1,0 mg/dl, Grade 4 < 1,0 mg/dl); hypokalaemia (Grade 3 < 3,0 – 2,5 mmol/l, Grade 4 < 2,5 mmol/l).

Table 4 shows laboratory findings from SPRYCEL clinical trials in which 2 182 patients with CML and imatinib resistance or intolerance received SPRYCEL for a median of 15 months. The haematology parameters for chronic phase CML patients are based on a minimum follow-up of 60 months.

Table 4: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML: Resistance or Intolerance to Prior Imatinib Therapy

	Chronic Phase (n = 1150)	**Accelerated Phase (n = 502)**	**Myeloid Blast Phase (n = 280)**	**Lymphoid Blast Phase (n = 115)**	**Ph+ ALL (n = 135)**
		Percent (%) of Patients			

Haematology Parameters*					
Neutropenia	48	69	80	83	75
Thrombocytopenia	42	72	82	86	71
Anaemia	19	55	75	51	42
Biochemistry Parameters					
Hypophosphataemia	10	14	20	19	21
Hypokalaemia	3	10	20	13	16
Hypocalcaemia	2	8	16	14	9
Elevated SGPT (ALT)	1	4	6	7	7
Elevated SGOT (AST)	1	1	4	5	4
Elevated Bilirubin	1	1	4	7	2
Elevated Creatinine	1	1	4	2	0

*Haematology parameters for chronic phase CML reflect 60-month follow-up.

CTC grades: neutropenia (Grade 3 ≥ 0,5 – < 1,0 × 10^9/l, Grade 4 < 0,5 × 10^9/l); thrombocytopenia (Grade 3 ≥ 25 – < 50 × 10^9/l, Grade 4 < 25 × 10^9/l); anaemia (haemoglobin Grade 3 ≥ 65 – < 80 g/l, Grade 4 < 65 g/l); elevated creatinine (Grade 3 > 3 – 6 × upper limit of normal range (ULN), Grade 4 > 6 × ULN); elevated bilirubin (Grade 3 > 3 – 10 × ULN, Grade 4 > 10 × ULN); elevated SGOT or SGPT (Grade 3 > 5 – 20 × ULN, Grade 4 > 20 × ULN); hypocalcaemia (Grade 3 < 7,0 – 6,0 mg/dl, Grade 4 < 6,0 mg/dl); hypophosphataemia (Grade 3 < 2,0 – 1,0 mg/dl, Grade 4 < 1,0 mg/dl); hypokalaemia (Grade 3 < 3,0 – 2,5 mmol/l, Grade 4 < 2,5 mmol/l).

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

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

Biochemistry:

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption.

In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

Post-marketing experience:

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

Infections and infestations: Hepatitis B reactivation

Cardiac disorders: Atrial fibrillation/atrial flutter[a], Ventricular tachydysrhythmias*†

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome[b], Toxic epidermal necrolysis, Erythema multiforme,

Vascular disorders: Thrombotic microangiopathy (TMA)

Renal and urinary disorders: Nephrotic syndrome

Nervous system disorders: Cerebrovascular accident†, Transient ischaemic attack, Ischaemic stroke†, Cerebral infarction

[a] Typically reported in elderly patients or in patients with confounding factors including significant underlying or concurrent cardiac or cardiovascular disorders, or other significant comorbidities (e.g.,

severe infection/sepsis, electrolyte abnormalities).

[b] In the postmarketing setting, individual cases of Steven's-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to SPRYCEL or to concomitant medications.

* Includes multiple adverse reaction terms.

† Includes events with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. Overdose of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since SPRYCEL is associated with severe myelosuppression (see section **4.4 Special warnings and precautions for use**), patients who ingest more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases (SRC, LCK, YES, FYN), along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases,

and PDGFβ receptor. Dasatinib inhibits the BCR-ABL kinase at a concentration of 0,6 –to 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.

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 (CNS).

5.2 Pharmacokinetic properties

Absorption:

Dasatinib is absorbed in patients following oral administration with peak concentrations between 0,5 and 6 hours. Following oral administration, the increase in the mean exposure (AUC_{τ}) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily. The overall mean terminal half-life of dasatinib is approximately 5 to 6 hours in patients.

Data from healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14 % increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21 % increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant. Dasatinib exposure variability is higher under fasted conditions (47 % CV) compared to light-fat meal (39 % CV) and high-fat meal (32 % CV) conditions.

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

Distribution:

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

Metabolism

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib. In healthy subjects administered 100 mg of [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29 % of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product.

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.

Special populations:

Renal Impairment: Since the renal clearance of dasatinib and its metabolites is < 4 %, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment*:* Since dasatinib is mainly metabolised through the liver, exposure to dasatinib is expected to increase if liver function is impaired. SPRYCEL should be used with caution in patients with

hepatic impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, Opadry® white. Opadry® white contains: hypromellose 6 cP, titanium dioxide and polyethylene glycol 400.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Keep well closed after first opening.

6.5 Nature and contents of container

SPRYCEL 20, 50, 70 mg film-coated tablets are packaged in white square, high density polyethylene (HDPE) bottles with white two-piece child-resistant, continuous thread (CRCT) closures having an aluminium foil induction seal (inner seal). Each bottle contains 60 tablets. The bottles will contain a cotton coiler and one silica gel desiccant canister.

SPRYCEL 100 mg film-coated tablets are packaged in white square, high density polyethylene (HDPE) bottles with white two-piece child-resistant, continuous thread (CRCT) closures having an aluminium foil induction seal (inner seal). Each bottle contains 30 tablets. The bottles will contain one silica gel desiccant canister.

6.6 Special precautions for handling and disposal

The use of gloves when handling the tablets is recommended, especially if the tablets are crushed or broken. Healthcare professionals should wear disposable chemotherapy gloves for appropriate disposal in order to minimise the risk of dermal exposure. Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd*

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria, 0157

8 REGISTRATION NUMBERS

SPRYCEL 20 mg tablets: 41/26/1039

SPRYCEL 50 mg tablets: 41/26/1040

SPRYCEL 70 mg tablets: 41/26/1041

SPRYCEL 100 mg tablets: 44/26/0205

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Sprycel 20 mg Tablets: 8 February 2008

Sprycel 50 & 70 mg Tablet: 9 December 2008

Sprycel 100 mg Tablet: 7 December 2012

10 DATE OF REVISION OF THE TEXT

12 October 2023

** Authorised user of the trademark SPRYCEL.*