# הודעה על החמרה ( מידע בטיחות) בעלון לרופא

# (מעודכן 05.2013)

**תאריך 26.1.2015**

**שם תכשיר באנגלית ומספר רישום (31919-21, 33125 Sprycel 20, 50, 70 and 100mg (**

**שם בעל הרישוםBRISTOL-MYERS SQUIBB (ISRAEL)**

טופס זה מיועד לפרוט ההחמרות בלבד !

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| **ההחמרות המבוקשות** |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **Special Warnings and Special Precautions for Use** | 4.4 Special warnings and precautions for useClinically relevant interactionsDasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolized primarily by or modulate the activity of CYP3A4 (see section 4.5).Concomitant use of dasatinib and medicinal products that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, coadministration of a potent CYP3A4 inhibitor is not recommended (see section 4.5)....Important adverse reactions*Myelosuppression*Treatment with dasatinib is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In imatinib resistant or intolerant patients, complete blood counts should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. In patients with newly diagnosed chronic phase CML, complete blood counts should be performed every 2 weeks for the first 6 weeks, every 3 months for 2 years and then every 6 months thereafter. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction (see sections 4.2 and 4.8).*Bleeding*In the Phase III study in patients with newly diagnosed chronic phase CML, 1 patient (< 1%) receiving dasatinib compared to 2 patients (1%) receiving imatinib had grade 3 or 4 haemorrhage after a minimum of 12 months follow-up. In clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe central nervous system (CNS) haemorrhage occurred in < 1% of patients. Eight cases were fatal and 6 of them were associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4% of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruptions and transfusions. Other grade 3 or 4 haemorrhage occurred in 2% of patients with resistance or intolerance to prior imatinib therapy. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopenia (see section 4.8). Additionally, in vitro and in vivo platelet assays suggest that SPRYCEL treatment reversibly affects platelet activation.Patients were excluded from participation in initial SPRYCEL clinical studies if they took medicinal products that inhibit platelet function or anticoagulants. In subsequent studies, the use of anticoagulants, acetylsalicylic acid, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with SPRYCEL if the platelet count was > 50,000‑75,000/mm3. 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 2 patients (1%) in each of the dasatinib and the imatinib-treatment groups after a minimum of 12 months follow-up (see section 4.8). In clinical studies in patients with resistance or intolerance to prior imatinib therapy, grade 3 or 4 fluid retention was reported in 11% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 2% of patients, respectively. In these studies, grade 3 or 4 ascites and generalised oedema were each reported in < 1% of patients, and grade 3 or 4 pulmonary oedema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics and short courses of steroids (see sections 4.2 and 4.8). While the safety profile of SPRYCEL in the older people 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. Fluid retention was reported less frequently in patients treated with once daily schedule compared to twice daily in two Phase III dose‑optimisation studies (see section 4.8)....*Cardiac adverse reactions*Dasatinib was studied in a randomised trial of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction and fatal myocardial infarction were reported in patients taking dasatinib. Adverse cardiac events were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath, and diaphoresis.... | 4.4 Special warnings and precautions for useClinically relevant interactionsDasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolized primarily by or modulate the activity of CYP3A4 (see section 4.5).Concomitant use of dasatinib and medicinal products or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, coadministration of a potent CYP3A4 inhibitor is not recommended (see section 4.5)....Important adverse reactions*Myelosuppression*Treatment with dasatinib is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In patients with advanced phase CML or Ph+ ALL, complete blood counts should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. In patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3months thereafter or as clinically indicated. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction (see sections 4.2 and 4.8).*Bleeding*In patients with chronic phase CML (n=548), 5 patients (1%) receiving dasatinib had grade 3 or 4 haemorrhage. In clinical studies in patients with advanced phase CML receiving the recommended dose of SPRYCEL (n=304), severe central nervous system (CNS) haemorrhage occurred in 1% of patients. One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 6% of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 haemorrhage occurred in 2% of patients with advanced phase CML. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopenia (see section 4.8). Additionally, *in vitro* and *in vivo* platelet assays suggest that SPRYCEL treatment reversibly affects platelet activation.Caution should be exercised if patients are required to take medicinal products that inhibit platelet function or anticoagulants.*Fluid retention*Dasatinib is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, grade 3 or 4 fluid retention was reported in 13 patients (5%) in the dasatinib-treatment group and in 2 patients (1%) in the imatinib-treatment group after a minimum of 60 months follow-up (see section 4.8). In all SPRYCEL treated patients with chronic phase CML, severe fluid retention occurred in 32 patients (6%) receiving SPRYCEL at the recommended dose (n=548). In clinical studies in patients with advanced phase CML receiving SPRYCEL at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 1% of patients, respectively. In these patients grade 3 or 4 pulmonary oedema and pulmonary hypertension were each reported in 1% of patients.Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics and short courses of steroids (see sections 4.2 and 4.8). Patients aged 65 years and older are more likely than younger patients to experience pleural effusion, dyspnoea, cough, pericardial effusion and congestive heart failure, and should be monitored closely....*Cardiac adverse reactions*Dasatinib was studied in a randomised trial of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Adverse cardiac events were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath, and diaphoresis.... |
| 4.5 Interaction with other medicinal products and other forms of interaction | Active substances that may increase dasatinib plasma concentrationsIn vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products which potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended.... | 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.... |
| 4.8 Undesirable effects | 1. Summary of the safety profile

...The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade. In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for adverse reactions in 5% of SPRYCEL-treated patients and 4% of imatinib-treated patients with a minimum of 12 months follow-up. After a minimum of 48 months follow-up, the cumulative discontinuation rates were 12% and 7%, respectively. Among patients with resistance or intolerance to prior imatinib therapy, the rates of discontinuation for adverse reactions at 2 years were 15% in chronic phase CML for all dosages, 16% in accelerated phase CML, 15% in myeloid blast phase CML, 8% in lymphoid blast phase CML and 8% in Ph+ ALL. In the Phase III dose-optimisation study in patients with chronic phase CML with a minimimum of 60 months follow-up, the rate of discontinuation for adverse reactions was 18% for patients treated with 100 mg once ...Based on a minimum of 12 months follow-up the most frequently reported adverse reactions in SPRYCEL-treated patients with newly diagnosed chronic phase CML were fluid retention (including pleural effusion) (19%), diarrhoea (17%), headache (12%), rash (11%), musculoskeletal pain (11%), nausea (8%), fatigue (8%), myalgia (6%), vomiting (5%), and muscle inflammation (4%). After a minimum of 48 months follow-up the cumulative rates for headache (13%), rash (13%), musculoskeletal pain (13%), nausea (11%), fatigue (10%), myalgia (7%), vomiting (5%), and muscle inflammation or spasms (5%) increased by ≤ 3% Cumulative rates of fluid retention and diarrhoea were 35% and 22%, respectively. The most frequently reported adverse reactions in SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, headache, nausea, skin rash, dyspnoea, haemorrhage, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy....b. Tabulated summary of adverse reactions...

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| **Table 2: Tabulated summary of adverse reactions**  |
| **Infections and infestations** |
| *Very common* | infection (including bacterial, viral, fungal, non-specified) |
| *Common* | pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection sepsis (including uncommon cases with fatal outcomes) |
|  |  |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** |
| *Uncommon* | tumour lysis syndrome |
| **Blood and lymphatic system disorders** |
| *Common* | febrile neutropenia, pancytopenia |
| *Rare* | aplasia pure red cell |
| **Immune system disorders** |
| *Uncommon* | hypersensitivity (including erythema nodosum) |
| **Metabolism and nutrition disorders** |
| *Common* | anorexia, appetite disturbances, hyperuricaemia, |
| *Uncommon* | , hypoalbuminemia |
| **Psychiatric disorders** |
| *Common* | depression, insomnia |
| *Uncommon* | anxiety, confusional state, affect lability, libido decreased |
| **Nervous system disorders** |
| *Very common* | Headache |
| *Common* | neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence |
| *Uncommon* | CNS bleeding\*a, syncope, tremor, amnesia |
| *Rare* | cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis |
| **Eye disorders** |
| *Common* | visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye |
| *Uncommon* | Conjunctivitis |
| *Rare* | visual impairment |
| **Ear and labyrinth disorders** |
| *Common* | Tinnitus |
| *Uncommon* | Vertigo |
| **Cardiac disorders** |
| *Common* | congestive heart failure/cardiac dysfunction\*b, pericardial effusion\*, arrhythmia (including tachycardia), palpitations |
| *Uncommon* | myocardial infarction (including fatal outcome)\*, electrocardiogram QT prolonged\*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly |
| *Rare* | cor pulmonale, myocarditis, acute coronary syndrome |
| *Not known* | atrial fibrillation/atrial flutter |
| **Vascular disorders** |
| *Very common* | haemorrhage\*c |
| *Common* | hypertension, flushing |
| *Uncommon* | hypotension, thrombophlebitis |
| *Rare* | livedo reticularis |
| *Not known* | thrombosis/embolism (including pulmonary embolism, deep vein thrombosis) |
| **Respiratory, thoracic and mediastinal disorders** |
| *Very common* | pleural effusion\*, dyspnoea, cough |
| *Common* | pulmonary oedema\*, pulmonary hypertension\*, lung infiltration, pneumonitis |
| *Uncommon* | bronchospasm, asthma |
| *Rare* | acute respiratory distress syndrome |
| *Not known* | interstitial lung disease, pulmonary arterial hypertension (pre-capillary pulmonary arterial hypertension) |
| **Gastrointestinal disorders** |
| *Very common* | diarrhoea, vomiting, nausea, abdominal pain |
| *Common* | gastrointestinal bleeding\*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder |
| *Uncommon* | pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites\*, anal fissure, dysphagia |
| *Rare* | protein-losing gastroenteropathy, ileus |
| *Not known* | fatal gastrointestinal haemorrhage\* |
| **Hepatobiliary disorders**  |
| *Uncommon* | hepatitis, cholecystitis, cholestasis |
| **Skin and subcutaneous tissue disorders** |
| *Very common* | skin rashd |
| *Common* | alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis |
| *Uncommon* | acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome |
| **Musculoskeletal and connective tissue disorders** |
| *Very common* | musculoskeletal pain |
| *Common* | arthralgia, myalgia, , muscular weakness, musculoskeletal stiffness, muscle spasm |
| *Uncommon* | rhabdomyolysis, muscle inflammation, tendonitis |
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| **Renal and urinary disorders** |
| *Uncommon* | renal failure, urinary frequency, proteinuria |
| **Reproductive system and breast disorders** |
| *Uncommon* | gynecomastia, irregular menstruation |
| **General disorders and administration site conditions** |
| *Very common* | fluid retention\*, fatigue, superficial oedema\*e, pyrexia  |
| *Common* | asthenia, pain, chest pain, generalised oedema\*, chills |
| *Uncommon* | malaise, temperature intolerance |
| **Investigations** |
| *Common* | weight decreased, weight increased |
| *Uncommon* | blood creatine phosphokinase increased |
| **Injury, poisoning, and procedural complications** |
| *Common* | Contusion |

a Includes cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.b Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure.c 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.d Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation and urticaria vesiculosa.e Includes auricular swelling, conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, genital swelling, gravitational oedema, incision site oedema lip oedema, localised oedema, macular oedema, oedema genital, oedema mouth, oedema peripheral, orbital oedema, penile oedema, periorbital oedema, pitting oedema, scrotal oedema, skin swelling swelling face and tongue oedema.\* For additional details, see section c"Description of selected adverse reactions".c. Description of selected adverse reactions*Myelosuppression*Treatment with SPRYCEL is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (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 12 months follow-up, only,, grade 1 and 2 pleural effusion were reported in 26 patients (10%) receiving SPRYCEL. The median time to onset was 28 weeks (range 4‑88 weeks). The median duration of pleural effusion was 50 days (range 5‑585 days). This reaction 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 pleural effusion, 73% had a dose interruption for a median of 15 days (6‑56 days). Thirty one percent had a dose reduction. Additionally, 46% received concomitant diuretics (median duration 64 days) and 27% received concomitant corticosteroids (median duration 29 days). A single patient underwent a therapeutic thoracentesis. With appropriate medical care, 23 patients (88% of those with pleural effusion) were able to continue on SPRYCEL and efficacy was not affected (92% achieved a complete cytogenetic response). Other fluid retention adverse reactions reported in patients taking SPRYCEL were superficial localised oedema (9%), and generalised oedema (2%). Congestive heart failure/cardiac dysfunction, pericardial effusions, pulmonary hypertension and pulmonary oedema were also reported in < 2% of patients. The cumulative rate of drug-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, and 24% at 48 months. The cumulative rates of superficial localised oedema and generalised oedema were 13% and 4%, respectively. The cumulative rates of congestive heart failure/cardiac dysfunction and pulmonary oedema were 2% and 1%, respectively, and the cumulative rates of pericardial effusions and pulmonary hypertension were 3% after a minimum of 48 months follow-up....*Cardiac adverse reactions*......In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL (median duration of treatment of 14 months for accelerated phase CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL), fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with SPRYCEL 140 mg once daily than in those treated with 70 mg twice daily (Table 3b)....Laboratory test abnormalities:*Haematology* In the Phase III newly diagnosed chronic phase CML study, the following grade 3 or 4 laboratory abnormalities were reported after a minimum of 12 months follow-up in patients taking SPRYCEL: neutropenia (21%), thrombocytopenia (19%), and anaemia (10%). After a minimum of 48 months follow-up, the cumulative rates of neutropenia, thrombocytopenia, and anaemia were 25%, 20% and 12%, 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 patientsafter a minimum of 12 months follow-up. After a minimum of 36 48 months follow-up the cumulative rate of permanent discontinuation due to grade 3 or 4 myelosuppression was 2.3%.In patients with CML with resistance or intolerance to prior imatinib therapy, cytopenias (thrombocytopenia, neutropenia, and anaemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 4.

| Table 4: CTC grades 3/4 haematological laboratory abnormalities in clinical studies in patients with resistance or intolerance to prior imatinib therapy  |
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|  | Chronic Phase(n= 1,150) | Accelerated Phase(n= 502) | Myeloid Blast Phase(n= 280) | Lymphoid Blast Phase andPh+ ALL(n= 250) |
|  | Percent (%) of Patients |
| **Haematology parameters** |  |  |  |  |
|  Neutropenia | 48 | 69 | 80 | 79 |
| Thrombocytopenia | 42 | 72 | 82 | 78 |
|  Anaemia | 19 | 55 | 75 | 46 |
| CTC grades: neutropenia (Grade 3 ≥ 0.5– < 1.0 × 109/l, Grade 4 < 0.5 × 109/l); thrombocytopenia (Grade 3 ≥ 25 – < 50 × 109/l, Grade 4 < 25 × 109/l); anaemia (haemoglobin Grade 3 ≥ 65 – < 80 g/l, Grade 4 < 65 g/l). |

...*Biochemistry*In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphatemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in ≤ 1% of patientsafter a minimum of 12 months follow-up. After a minimum of 48 months follow-up the cumulative rate of grade 3 or 4 hypophosphatemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained < 1%..There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.*2 year follow-up*Grade 3 or 4 elevations of transaminases or bilirubin were reported in < 1% of patients with chronic phase CML (resistant or intolerant to imatinib), but elevations were reported with an increased frequency of 1 to 7% of patients with advanced phase CML and Ph+ ALL. It was usually managed with dose reduction or interruption. In the Phase III dose-optimisation study in chronic phase CML, grade 3 or 4 elevations of transaminases or bilirubin were reported in ≤ 1% of patients with similar low incidence in the four treatment groups. In the Phase III dose-optimisation study in advanced phase CML and Ph+ALL, grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% to 4% of patients across treatment groups.Approximately 5% of the SPRYCEL-treated patients who had normal baseline levels experienced grade 3 or 4 transient hypocalcaemia at some time during the course of the study. In general, there was no association of decreased calcium with clinical symptoms. Patients developing grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation. Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in < 1% of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.d. Other special populationWhile the safety profile of SPRYCEL in the older people 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 (see section 4.4). | Summary of the safety profile...The majority of SPRYCEL-treated patients experienced adverse reactions at some time. In the overall population of 2,712 SPRYCEL treated patients, 520 (19%) experienced adverse reactions leading to treatment discontinuation. Most reactions were of mild-to-moderate grade.In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for adverse reactions in 5% of SPRYCEL-treated patients and 4% of imatinib-treated patients with a minimum of 12 months follow-up. After a minimum of 60 months follow-up, the cumulative discontinuation rates were 14% and 7%, respectively. Among the 1,618 dasatinib-treated patients with chronic phase CML, adverse reactions leading ~~to~~ discontinuation were reported in 329 (20.3%) patients, and among the 1,094 dasatinib-treatedpatients with advanced phase disease, adverse reactions leading to discontinuation were reported in 191 (17.5%) patients....Based on a minimum of 12 months follow-up the most frequently reported adverse reactions in SPRYCEL-treated patients with newly diagnosed chronic phase CML were fluid retention (including pleural effusion) (19%), diarrhoea (17%), headache (12%), rash (11%), musculoskeletal pain (11%), nausea (8%), fatigue (8%), myalgia (6%), vomiting (5%), and muscle inflammation (4%). After a minimum of 60 months follow-up the cumulative rates for rash (14%), musculoskeletal pain (14%), headache (13%), fatigue (11%), nausea (10%), myalgia (7%), vomiting (5%), and muscle inflammation or spasms (5%) increased by ≤ 3%. Cumulative rates of fluid retention and diarrhoea were 39% and 22%, respectively. The most frequently reported adverse reactions in SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, headache, nausea, skin rash, dyspnoea, haemorrhage, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of SPRYCEL-treated patients with resistance or intolerance to prior imatinib therapy....Tabulated summary of adverse reactions...

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| **Table 2: Tabulated summary of adverse reactions** |
| **Infections and infestations** |
| *Very common* | infection (including bacterial, viral, fungal, non-specified) |
| *Common* | pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon cases with fatal outcomes) |
|  |  |
| **~~Neoplasms benign, malignant and unspecified (including cysts and polyps)~~** |
| *~~Uncommon~~* | ~~tumour lysis syndrome~~ |
| **Blood and lymphatic system disorders** |
| *Very Common* | myelosuppression (including anemia, neutropenia, thrombocytopenia) |
| *Common* | febrile neutropenia |
| *Uncommon* | lymphadenopathy, lymphopenia |
| *Rare* | aplasia pure red cell |
| **Immune system disorders** |
| *Uncommon* | hypersensitivity (including erythema nodosum) |
| **Endocrine Disorders** |
| *Uncommon* | hypothyroidism |
| *Rare* | hyperthyroidism, thyroiditis |
| **Metabolism and nutrition disorders** |
| *Common* | ~~anorexia~~, appetite disturbancesa, hyperuricaemia |
| *Uncommon* | tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia |
| *Rare* | diabetes mellitus |
| **Psychiatric disorders** |
| *Common* | depression, insomnia |
| *Uncommon* | anxiety, confusional state, affect lability, libido decreased |
| **Nervous system disorders** |
| *Very common* | headache |
| *Common* | neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence |
| *Uncommon* | CNS bleeding\*b, syncope, tremor, amnesia, balance disorder |
| *Rare* | cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia |
| **Eye disorders** |
| *Common* | visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye |
| *~~Uncommon~~* | ~~Conjunctivitis~~ |
| *Uncommon* | visual impairment, conjunctivitis, photophobia, lacrimation increased |
| **Ear and labyrinth disorders** |
| *Common* | Tinnitus |
| *Uncommon* | hearing loss, vertigo |
| **Cardiac disorders** |
| *Common* | congestive heart failure/cardiac dysfunction\*c, pericardial effusion\*, arrhythmia (including tachycardia), palpitations |
| *Uncommon* | myocardial infarction (including fatal outcome)\*, electrocardiogram QT prolonged\*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased |
| *Rare* | cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis |
| *Not known* | atrial fibrillation/atrial flutter |
| **Vascular disorders** |
| *Very common* | haemorrhage\*d |
| *Common* | hypertension, flushing |
| *Uncommon* | hypotension, thrombophlebitis |
| *~~Rare~~* | ~~livedo reticularis~~ |
| *Rare~~Not known~~* | ~~thrombosis/embolism (including pulmonary embolism~~, deep vein thrombosis, embolism, livedo reticularis |
| **Respiratory, thoracic and mediastinal disorders** |
| *Very common* | pleural effusion\*, dyspnoea, ~~cough~~ |
| *Common* | pulmonary oedema\*, pulmonary hypertension\*, lung infiltration, pneumonitis, cough |
| *Uncommon* | pulmonary arterial hypertension, bronchospasm, asthma |
| *Rare* | pulmonary embolism, acute respiratory distress syndrome |
| *Not known* | interstitial lung disease, ~~pulmonary arterial hypertension (pre-capillary pulmonary arterial hypertension)~~ |
| **Gastrointestinal disorders** |
| *Very common* | diarrhoea, vomiting, nausea, abdominal pain |
| *Common* | gastrointestinal bleeding\*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder |
| *Uncommon* | pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites\*, anal fissure, dysphagia, gastroesophageal reflux disease |
| *Rare* | protein-losing gastroenteropathy, ileus, anal fistula |
| *Not known* | fatal gastrointestinal haemorrhage\* |
| **Hepatobiliary disorders**  |
| *Uncommon* | hepatitis, cholecystitis, cholestasis |
| **Skin and subcutaneous tissue disorders** |
| *Very common* | skin rashe~~rash~~~~d~~ |
| *Common* | alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis |
| *Uncommon* | neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder |
| *Rare* | leukocytoclastic vasculitis, skin fibrosis |
| *Not known* | Stevens-Johnson Syndromef |
| **Musculoskeletal and connective tissue disorders** |
| *Very common* | musculoskeletal pain |
| *Common* | arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm |
| *Uncommon* | rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis |
| **Renal and urinary disorders** |
| *Uncommon* | renal impairment (including renal failure), urinary frequency, proteinuria |
| **Pregnancy, puerperium and perinatal conditions** |
| *Rare* | Abortion |
| **Reproductive system and breast disorders** |
| *Uncommon* | gynecomastia, menstrual disorder~~irregular menstruation~~ |
| **General disorders and administration site conditions** |
| *Very common* | peripheral oedemag,~~fluid retention\*,~~ fatigue, ~~superficial oedema\*~~~~e~~, pyrexia, face oedemah  |
| *Common* | asthenia, pain, chest pain, generalised oedema\*i, chills |
| *Uncommon* | malaise, other superficial oedemaj~~temperature intolerance~~ |
| *Rare* | gait disturbance |
| **Investigations** |
| *Common* | weight decreased, weight increased |
| *Uncommon* | blood creatine phosphokinase increased, gamma-glutamyltransferase increased |
| **Injury, poisoning, and procedural complications** |
| *Common* | Contusion |

a Includes decreased appetite, early satiety, increased appetite.b Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.c Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure,cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.d Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.e Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriaisis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.f gravitational oedema, localised oedema, oedema peripheral.g in the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to SPRYCEL or to concomitant medications.h conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbitalo edema, swelling face.i fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.j genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.\* For additional details, see section "Description of selected adverse reactions"Description of selected adverse reactions*Myelosuppression*Treatment with SPRYCEL is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (see section 4.4). **...***Fluid retention*Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”. In the newly diagnosed chronic phase CML study after a minimum of 60 months follow-up, dasatinib-related fluid retention events includedpleural effusion (28%), superficial oedema (14%), pulmonary hypertension (5%), generalised oedema (4%), and pericardial effusion (4%). Congestive heart failure/cardiac dysfunction and pulmonary oedema were reported in < 2% of patients.The cumulative rate of dasatinib-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, 24% at 48 months and 28% at 60 months. A total of 46 dasatinib-treated patients had recurrent pleural effusions. Seventeen patients had 2 separate events, 6 had 3 events, 18 had 4 to 8 events and 5 had > 8 episodes of pleural effusions.The median time to first dasatinib-related grade 1 or 2 pleural effusion was 114weeks (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....*Cardiac adverse reactions*...**Table 3a: Selected adverse reactions reported in a phase 3~~III~~ dose optimisation study (Imatinib intolerant or resistant Chronic Phase CML)**a **~~(minimum of 24 months follow-up)~~**...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 of140 mg once daily are shown in Table 3b.A 70 mg twice daily regimen was also studied. The 140 mg once daily regimen showed a comparable efficacy profile to the 70 mg twice daily regimen but a more favorable safety profile~~.~~...Laboratory test abnormalities*Haematology* In the Phase III newly diagnosed chronic phase CML study, the following grade 3 or 4 laboratory abnormalities were reported after a minimum of 12 months follow-up in patients taking SPRYCEL: neutropenia (21%), thrombocytopenia (19%), and anaemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropenia, thrombocytopenia, and anaemia were 29%, 22% and 13%, respectively.In SPRYCEL-treated patients with newly diagnosed chronic phase CML who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 1.6% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of permanent discontinuation due to grade 3 or 4 myelosuppression was 2.3%.In patients with CML with resistance or intolerance to prior imatinib therapy, cytopenias (thrombocytopenia, neutropenia, and anaemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 haematological abnormalities is presented in Table 4. ...*Biochemistry* In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphatemia was reported in 4% of SPRYCEL-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in ≤ 1% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up the cumulative rate of grade 3 or 4 hypophosphatemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained 1%. There were no discontinuations of SPRYCEL therapy due to these biochemical laboratory parameters.*2 year follow-up*Grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% of patients with chronic phase CML (resistant or intolerant to imatinib), but elevations were reported with an increased frequency of 1 to 7% of patients with advanced phase CML and Ph+ ALL. It was usually managed with dose reduction or interruption. In the Phase III dose-optimisation study in chronic phase CML, grade 3 or 4 elevations of transaminases or bilirubin were reported in ≤ 1% of patients with similar low incidence in the four treatment groups. In the Phase III dose-optimisation study in advanced phase CML and Ph+ALL, grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% to 5% of patients across treatment groups.Approximately 5% of the SPRYCEL-treated patients who had normal baseline levels experienced grade 3 or 4 transient hypocalcaemia at some time during the course of the study. In general, there was no association of decreased calcium with clinical symptoms. Patients developing grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation. Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in < 1% of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.Other special populationWhile the safety profile of SPRYCEL in older people was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions such as fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance and more likely to experience less frequently reported adverse reactions such as abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease and should be monitored closely (see section 4.4).Reporting of suspected adverse reactionsReporting 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  |
| 5.PHARMACOLOGICAL PROPERTIES | 5.1 Pharmacodynamic properties*Chronic Phase CML - Newly Diagnosed***…**With a minimum of 48 months follow-up, 67% of patients randomised to the SPRYCEL group and 65% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation within 48 months due to disease progression occurred in 7% of SPRYCEL-treated patients and 7% of imatinib-treated patients.Efficacy results are presented in Table 5. A statistically significantly greater proportion of patients in the SPRYCEL group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of SPRYCEL was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

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| --- |
| Table 5: Efficacy results in newly diagnosed patients with Chronic Phase CML  |
|  | SPRYCELn= 259 | imatinibn= 260 | p-value |
|  | **Response rate (95% CI)** |  |
| **Cytogenetic response**  |  |  |  |
| **within 12 months** |  |  |  |
|  cCCyRa  | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) | p< 0.007\* |
|  CCyRb | 85.3% (80.4-89.4) | 73.5% (67.7-78.7) | ⎯ |
| **within 24 months** |  |  |  |
| cCCyRa | 80.3% | 74.2% | ⎯ |
| CCyRb | 87.3% | 82.3% | ⎯ |
| **within 36 months** |  |  |  |
| cCCyRa | 82.6% | 77.3% | ⎯ |
| CCyRb | 88.0% | 83.5% | ⎯ |
| **within 48 months** |  |  |  |
| cCCyRa | 82.6% | 78.5% | ⎯ |
| CCyRb | 87.6% | 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) | ⎯ |
|  | **Hazard Ratio**  |  |
|  | **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) | ⎯ |
|  |

a Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart). b Complete cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation.c Major molecular response (at any time) was defined as BCR-ABL ratios ≤ 0.1% by RQ-PCR in peripheral blood samples standardized 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 intervalAfter 48 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 48 months of follow-up was 9.2  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 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: 70% and 63%; high risk: 65% and 52%, respectively).In an exploratory analysis, more dasatinib-treated subjects (84%) achieved early molecular response (defined as BCR-ABL levels ≤ 10% at 3 months) compared with imatinib-treated subjects (64%). Subjects achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 6.

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| Table 6: Dasatinib Subjects with BCR-ABL ≤ 10% and > 10% at 3 Months |
| **Dasatinib N = 235** | **Subjects with BCR-ABL ≤ 10% at 3 Months** | **Subjects with BCR-ABL > 10% at 3 Months** |
| Number of Subjects (%) | 198 (84.3) | 37 (15.7) |
| Transformation at 48 months, n/N (%) | 6/198 (3.0) | 5/37 (13.5) |
| Rate of PFS at 48 Months (95% CI) | 93.3% (89.6, 97.0) | 72.9% (55.1, 90.7) |
| Rate of OS at 48 Months (95% CI) | 95.4% (92.5, 98.3) | 82.9% (70.4, 95.4) |

 | 5.1 Pharmacodynamic properties*Chronic Phase CML - Newly Diagnosed*...With a minimum of 60 months follow-up, 60% of patients randomised to the SPRYCEL group and 63% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation within 60 months due to disease progression occurred in 11% of SPRYCEL-treated patients and 14% of imatinib-treated patients.Efficacy results are presented in Table 5. A statistically significantly greater proportion of patients in the SPRYCEL group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of SPRYCEL was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

| Table 5: Efficacy results from a phase 3 study of newly diagnosed patients with Chronic Phase CML  |
| --- |
|  | SPRYCELn= 259 | imatinibn= 260 | p-value |
|  | **Response rate (95% CI)** |  |
| **Cytogenetic response**  |  |  |  |
| **within 12 months** |  |  |  |
|  cCCyRa  | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) | p< 0.007\* |
|  CCyRb | 85.3% (80.4‑89.4) | 73.5% (67.7‑78.7) | ⎯ |
| **within 24 months** |  |  |  |
| cCCyRa | 80.3% | 74.2% | ⎯ |
| CCyRb | 87.3% | 82.3% | ⎯ |
| **within 36 months** |  |  |  |
| cCCyRa | 82.6% | 77.3% | ⎯ |
| CCyRb | 88.0% | 83.5% | ⎯ |
| **within 48 months** |  |  |  |
| cCCyRa | 82.6% | 78.5% | ⎯ |
| CCyRb | 87.6% | 83.8% | ⎯ |
| **within 60 months** |  |  |  |
| cCCyRa | 83.0% | 78.5% | ⎯ |
| CCyRb | 88.0% | 83.8% | ⎯ |
| **Major Molecular Response**c |  |  |  |
| **12 months** | 52.1% (45.9–58.3) | 33.8% (28.1–39.9) | p< 0.00003\* |
| **24 months**  | 64.5% (58.3-70.3) | 50% (43.8-56.2) | ⎯ |
| **36 months** | 69.1% (63.1-74.7) | 56.2% (49.9-62.3) | ⎯ |
| **48 months** | 75.7% (70.0-80.8) | 62.7% (56.5-68.6) | ⎯ |
| **60 months** | 76.4% (70.8-81.5) | 64.2% (58.1-70.1) | p=0.0021 |
|  | **Hazard Ratio (HR)** |  |
|  | **within 12 months (99.99% CI)** |  |
| Time-to cCCyR | 1.55 (1.0‑2.3) | p< 0.0001\* |
| Time-to MMR | 2.01 (1.2‑3.4) | p< 0.0001\* |
| Durability of cCCyR | 0.7 (0.4‑1.4) | p< 0.035 |
|  | **within 24 months (95% CI)** |  |
| Time-to cCCyR | 1.49 (1.22-1.82) | ⎯ |
| Time-to MMR | 1.69 (1.34-2.12) | ⎯ |
| Durability of cCCyR | 0.77 (0.55-1.10) | ⎯ |
|  | **within 36 months (95% CI)** |  |
| Time-to cCCyR | 1.48 (1.22-1.80) | ⎯ |
| Time-to MMR | 1.59 (1.28-1.99) | ⎯ |
| Durability of cCCyR | 0.77 (0.53-1.11) | ⎯ |
|  | **within 48 months (95% CI)** |  |
| Time-to cCCyR | 1.45 (1.20-1.77) | ⎯ |
| Time-to MMR | 1.55 (1.26-1.91) | ⎯ |
| Durability of cCCyR | 0.81 (0.56-1.17) | ⎯ |
|  | **within 60 months (95% CI)** |  |
| Time-to cCCyR | 1.46 (1.20-1.77) | p=0.0001 |
| Time-to MMR | 1.54 (1.25-1.89) | p<0.0001 |
| Durability of cCCyR | 0.79 (0.55-1.13) | p=0.1983 |
| a Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart). b Complete cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation.c Major molecular response (at any time) was defined as BCR-ABL ratios ≤ 0.1% by RQ-PCR in peripheral blood samples standardised on the International scale. These are cumulative rates representing minimum follow-up for the timeframe specified.\*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.CI = confidence interval |

After 60 months of follow-up, median time to cCCyR was 3.1 months in the SPRYCEL group and 5.8 months in the imatinib group in patients with a confirmed CCyR. Median time to MMR after 60 months of follow-up was 9.3 months in the SPRYCEL group and 15.0 months in the imatinib group in patients with a MMR. These results are consistent with those seen at 12, 24 and 36 months. ...The rate of MMR at any time in each risk group determined by Hasford score was higher in the SPRYCEL group compared with the imatinib group (low risk: 90% and 69%; intermediate risk: 71% and 65%; high risk: 67% and 54%, respectively).In an additional analysis, more dasatinib-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels ≤ 10% at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 6. |
|  | 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 48-month PFS rate was 90.0% (CI: 86% - 94%) for both the dasatinib and imatinib treatment groups. At 48 months, transformation to accelerated or blast phase occurred in fewer dasatinib-treated patients (n = 8; 3%) compared with imatinib-treated patients (n = 14; 5%). The estimated 48-month survival rates for dasatinib and imatinib-treated patients were 93% (CI: 90% - 96%) and 92% (CI: 89% - 95%), respectively.**…***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***...**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%]). The main secondary endpoint of the study also showed comparable efficacy (non-inferiority) between the 100 mg total daily dose and the 140 mg total daily dose (difference in MCyR -0.2%; 95% confidence interval [-8.9% - 8.5%]). Efficacy results are presented in Table 8 and 9.

| **Table 9: Efficacy of SPRYCEL in phase III dose-optimisation study: Chronic Phase CML (5-year results)** |
| --- |
|  | **100 mg once daily** | 50 mg twice dailya | 140 mg once dailya | 70 mg twice dailya |
|  **All patients** | **n = 167** | n = 168 | n = 167 | n = 168 |
|  **Imatinib-resistant patients** | **n = 124** | n = 124 | n = 123 | n = 126 |
| **Survival (% [95% CI]; Kaplan-Meier estimates)** |
| Progression-Freeb |
|  1 Year |  |  |  |  |
|  All patients  | 90% (86‑95) | 86% (81‑92) | 88% (82‑93) | 87% (82‑93) |
|  Imatinib-resistant patients  | 88% (82‑94) | 84% (77‑91) | 86% (80‑93) | 85% (78‑91) |
|  2 Year |  |  |  |  |
|  All patients  | 80% (73‑87) | 76% (68‑83) | 75% (67‑82) | 76% (68‑83) |
|  Imatinib-resistant patients  | 77% (68‑85) | 73% (64‑82) | 68% (59‑78) | 72% (63‑81) |
|  5 Year |  |  |  |  |
|  All patients  | 51% (41-60) | 56% (47-65) | 42% (32-52) | 52% (44-61) |
|  Imatinib-resistant patients  | 49% (39-59) | 55% (44-65) | 33% (21-44) | 51% (41-61) |
| Overall Survival |
|  1 Year |  |  |  |  |
|  All patients  | 96% (93‑99) | 96% (93‑99) | 96% (93‑99) | 94% (90‑98) |
|  Imatinib-resistant patients  | 94% (90‑98) | 95% (91‑99) | 97% (93‑100) | 92% (87‑97) |
|  2 Year |  |  |  |  |
|  All patients  | 91% (86‑96) | 90% (86‑95) | 94% (90‑97) | 88% (82‑93) |
|  Imatinib-resistant patients  | 89% (84‑95) | 89% (83‑94) | 94% (89‑98) | 84% (78‑91) |
|  5 Year |  |  |  |  |
|  All patients  | 78% (72-85) | 75% (68-82) | 79% (72-86) | 73% (66-80) |
|  Imatinib-resistant patients  | 77% (69-85) | 73% (64-81) | 76% (66-85) | 70% (62-78) |
| a Not a recommended starting dose of SPRYCEL for chronic phase CML (see section 4.2).b Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, confirmed AP/BP disease or death. PFS was analysed on an intent-to-treat principle and patients were followed to events including subsequent therapy. |

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

|  |
| --- |
| **Table 9: Long Term Efficacy of SPRYCEL in phase 3 dose optimisation study: Imatinib Resistant or Intolerant Chronic Phase CML Patients** a |
|  | Minimum Follow-up Period |
|  | 1 year  | 2 years  | 5 years  | 7 years  |
| **Major Molecular Response** |
| All patients | NA | 37% (57/154) | 44% (71/160) | 46% (73/160) |
| Imatinib-resistant patients | NA | 35% (41/117) | 42% (50/120) | 43% (51/120) |
| Imatinib-intolerant patients | NA | 43% (16/37) | 53% (21/40) | 55% (22/40) |
| **Progression-Free Survival**b |
| All patients | 90% (86, 95) | 80% (73, 87) | 51% (41, 60) | 42% (33, 51) |
| Imatinib-resistant patients | 88% (82, 94) | 77% (68, 85) | 49% (39, 59) | 39% (29, 49) |
| Imatinib-intolerant patients | 97% (92, 100) | 87% (76, 99) | 56% (37, 76) | 51% (32, 67) |
| **Overall Survival** |
| All patients | 96% (93, 99) | 91% (86, 96) | 78% (72, 85) | 65% (56, 72) |
| Imatinib-resistant patients | 94% (90, 98) | 89% (84, 95) | 77% (69, 85) | 63% (53, 71) |
| Imatinib-intolerant patients | 100% (100, 100) | 95% (88, 100) | 82% (70, 94) | 70% (52, 82) |

a Results reported in recommended starting dose of 100 mg once daily.b Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, confirmed AP/BP disease or death. PFS was analysed on an intent-to-treat principle and patients were followed to events including subsequent therapy |
|  | **…**Based on the Kaplan-Meier estimates, the proportion of patients treated with dasatinib 100 mg once daily who maintained MCyR for 18 months was 93% (95% CI: [88%-98%]) and 88% (95% CI: [81%-95%]) for patients treated with 70 mg of dasatinib twice daily.In patients resistant to imatinib who received 100 mg once daily, major molecular response (MMR) in all patients assessed for MMR was achieved in 35% within 2 years and 42% within 5 years.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%. In the intolerant population receiving 100 mg once daily, MMR in all patients assessed for MMR was achieved in 43% within 2 years and 53% within 5 years Based on the Kaplan-Meier estimates, all imatinib-intolerant patients (100%) maintained MCyR for 1 year and 92% (95% CI: [80%-100%]) maintained MCyR for 18 months. The estimated rate of PFS in this population was 97% (95% CI: [92%-100%]) at 1 year and 87% (95% CI: [76%-99%]) at 2 years and 56% (95% CI: [37%-76%]) at 5 years. The estimated rate of overall survival was 100% at 1 year and 95% (95% CI: [88%-100%]) at 2 years and 82% (95% CI: [70%-94%]) at 5 years. 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%]). Response rates are presented in Table 10. | *...*Based on the Kaplan-Meier estimates, the proportion of patients treated with dasatinib 100 mg once daily who maintained MCyR for 18 months was 93% (95% CI: [88%-98~~%]).~~Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77% and CCyR in 67%. 2- In the study in advanced phase CML and Ph+ ALL, the primary endpoint was MaHR. A total of 611 patients were randomised to either the dasatinib 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range 0.03‑31 months).The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [‑7.1% - 8.7%]); however, the 140 mg once daily regimen demonstrated improved safety and tolerability.Response rates are presented in Table 10. |

# הודעה על החמרה ( מידע בטיחות) בעלון לצרכן

# (מעודכן 05.2013)

 **תאריך 26.1.2015**

**שם תכשיר באנגלית ומספר הרישום**

**Sprycel 20, 50, 70 and 100mg**

**140.30.31919, 140.31.31920, 140.32.31921, 143 90 33125**

**שם בעל הרישום Bristol-Myers Squibb Israel Ltd**.

טופס זה מיועד לפרוט ההחמרות בלבד !

|  |
| --- |
| **ההחמרות המבוקשות**  |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **2. לפני שימוש בתרופה:** | **שימוש בתרופה** **ומזון:**ניתן לקחת את התרופה עם האוכל או ללא אוכל. | **שימוש בתרופה** **ומזון:**ניתן לקחת את התרופה עם האוכל או ללא אוכל.אין ליטול את התרופה עם אשכוליות או מיץ אשכוליות  |
| **3. כיצד תשתמש בתרופה?** | תמיד יש להשתמש לפי הוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח. **המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.** יש ליטול את התרופה בזמן קבוע כל יום.יש לבלוע את הטבליות בשלמותן, אין לרסק את התרופה. ניתן לקחת את התרופה עם האוכל או ללא אוכל.... | תמיד יש להשתמש לפי הוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח. **המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.** יש ליטול את התרופה בזמן קבוע כל יום.יש לבלוע את הטבליות בשלמותן, אין לרסק את התרופה. ניתן לקחת את התרופה עם האוכל או ללא אוכל. אין ליטול את התרופה עם אשכוליות או מיץ אשכוליות... |
| **4. תופעות לוואי:**  | כמו בכל תרופה, השימוש בספרייסל עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן. **יש לפנות מיד לרופא אם מופיעות** התופעות הבאות אשר יכולות להיות סימנים של תופעות לוואי חמורות:כאב בחזה, קשיי נשימה, שיעול והתעלפות , דימום בלתי צפוי או שיש לך חבלות מבלי שנפצעת ; אם יש דם בהקאות, בצואה או בשתן שלך, או הופעה של צואה שחורה, אם מופיעים סימני זיהום כמו חום וצמרמורות חמורות. תופעות לוואי נוספות:תופעות לוואי נפוצות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה): זיהום ממקור חיידק/וירוס/פטרייה, קוצר נשימה, שיעול, שלשולים, בחילות והקאות, פריחה בעור, חום, נפיחות סביב הידיים והרגליים, כאב ראש, תחושת עייפות או חולשה, דימום, כאבים בשרירים, כאבי בטן. בדיקות מעבדה עשויות להראות: ספירת טסיות דם נמוכה, ספירת תאי דם לבנים נמוכה (ניוטרופניה), אנמיה, נוזלים סביב הריאות.תופעות לוואי נפוצות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100):דלקת ריאות, זיהום הרפס ויראלי, דלקות בדרכי הנשימה העליונות, זיהום חמור בדם או ברקמות, דפיקות לב, הסמקה, סחרחורת, אי ספיקת לב, הפרעות בתפקוד הלב, לחץ דם גבוה, לחץ דם מוגבר בעורקים הנכנסים לריאות ושינויים בעורקים הנכנסים לריאות, התנפחות בגוף כגון בקרסוליים, עייפות מיוחדת,הפרעות בתיאבון, הפרעות בחוש הטעם, גודש או נפיחות בבטן, דלקת של המעי הגס, עצירות, צרבת, כיבים בפה, עליה במשקל, ירידה במשקל, דלקת הקיבה, דלקת בעור, עקצוץ בעור, גירוד, עור יבש, אקנה, נשירת שיער, הזעה מוגברת, הפרעה בראיה כולל טשטוש ראיה, רעש מתמשך באוזניים, עין יבשה, שטפי דם, דכאון, נדודי שינה, חבלות, אנורקסיה, ישנוניות, בצקת כללית, כאב במפרקים, חולשת שרירים, דלקת שרירים, כאב בחזה, כאב באזור הידיים והרגליים, צמרמורת, כאב בטן, נוקשות שרירים ומפרקים, התכווצות שרירים.בדיקות מעבדה עשויות להראות: נוזלים סביב הלב, נוזלים בריאות, הפרעות בקצב הלב, נויוטרופניה פיברילית, חוסר בכל תאי הדם, דימום במערכת העיכול, רמות חומצה אוראית גבוהות בדם. תופעות לוואי שאינן נפוצות (תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000): התקף לב, דלקת הרירית המקיפה את הלב, קצב לב לא סדיר, כאבים בחזה בשל חוסר אספקת דם ללב (אנגינה), לחץ דם נמוך ,קשיי נשימה עקב הצרות קנה, אסטמה, דלקת של הלבלב ,כיב פפטי, דלקת בדרכי העיכול, בטן נפוחה, קרע בעור של התעלה האנאלית, קושי בבליעה, דלקת של כיס המרה, חסימה של צנרת כיס המרה, תגובה אלרגית כולל צברים אדומים ורגישים על העור (erythema nodosum) , חרדה, בלבול, שינויים במצב רוח, דחף מיני נמוך, עילפון, רעד ,דלקת של העין שגורמת לאדמומיות או לכאב, מחלת עור המתאפיינת ברבדים אדומים, רגישים, מוגדרים היטב המלווים בהתפרצות פתאומית של חום וספירת תאי דם לבנים גבוהה (acute febrile neutrophilic dermatosis) ,רגישות לאור ,שינוי בצבע העור, דלקת ברקמת השומן מתחת לעור,כיב בעור ,שלפוחיות בעור, שינוי בציפורניים, הפרעה ביד/רגל, אי ספיקת כליות, תכיפות במתן שתן, הגדלת חזה אצל גברים, וסת לא סדירה, חולשה ואי נוחות כללית, אי סבילות לטמפרטורה, דלקת ורידית העלולה לגרום לאדמומיות, רגישות ונפיחות , דלקת של הגיד, אובדן זיכרון.בדיקות עשויות להראות: תוצאות בדיקת דם לא תקינות ותפקוד כליות לקוי הנגרם מפינוי חומרי הפסולת של הגידול (tumour lysis syndrome) , רמות נמוכות של אלבומין בדם, דימום במוח, אי סדירות בפעילות החשמלית של הלב, לב מוגדל, דלקת של הכבד, חלבון בשתן, עלייה באנזים קריאטין פוספוקינאז**.**תופעות לוואי נדירות (תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000): הגדלה של חדר הלב הימני, דלקת של שריר הלב , מצבים שונים הנוצרים כתוצאה מחסימה של אספקת דם לשריר הלב (acute coronary syndrome), אובדן של חומרי תזונה חיוניים כמו חלבון ממערכת עיכול , חסימת מעיים, עוויתות , דלקת של עצב הראייה העלולה לגרום לאובדן מלא או חלקי של ראייה, פגיעה בראייה , גוון כחלחל-סגלגל של העור, שבץ, חוסר תפקוד נוירולוגי זמני כתוצאה מזרימת דם לקויה, שיתוק בעצב הפנים.בדיקות עשויות להראות : ייצור תאי דם אדומים בלתי מספק.תופעות לוואי נוספים שדווחו (בתדירות לא ידועה) כוללות: דלקת ריאות , שינויים בכלי הדם המובילים ריאות וקרישי דם בכלי הדם.אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא. | כמו בכל תרופה, השימוש בספרייסל עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.**יש לפנות מיד לרופא אם מופיעות** התופעות הבאות אשר יכולות להיות סימנים של תופעות לוואי חמורות:כאב בחזה, קשיי נשימה, שיעול והתעלפות , דימום בלתי צפוי או שיש לך חבלות מבלי שנפצעת ; אם יש דם בהקאות, בצואה או בשתן שלך, או הופעה של צואה שחורה, אם מופיעים סימני זיהום כמו חום וצמרמורות חמורות,חום, כאב גרון או פה, שלפוחיות או קילוף של העור ו / או ריריות.תופעות לוואי נוספות:תופעות לוואי נפוצות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה):זיהום ממקור חיידק/וירוס/פטרייה, קוצר נשימה, שלשולים, בחילות והקאות, פריחה בעור, חום, נפיחות סביב הפנים, הידיים והרגליים, כאב ראש, תחושת עייפות או חולשה, דימום, כאבים בשרירים, כאבי בטן. בדיקות מעבדה עשויות להראות: ספירת טסיות דם נמוכה, ספירת תאי דם לבנים נמוכה (ניוטרופניה), אנמיה, נוזלים סביב הריאות.תופעות לוואי נפוצות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100):דלקת ריאות, זיהום הרפס ויראלי, דלקות בדרכי הנשימה העליונות, זיהום חמור בדם או ברקמות, דפיקות לב, הפרעות בקצב הלב, הסמקה, סחרחורת, אי ספיקת לב, חולשה בשריר הלב, לחץ דם גבוה, יתר לחץ דם ריאתי , שיעול, התנפחות בגוף כגון בקרסוליים, עייפות מיוחדת,הפרעות בתיאבון, הפרעות בחוש הטעם, גודש או נפיחות בבטן, דלקת של המעי הגס, עצירות, צרבת, כיבים בפה, עליה במשקל, ירידה במשקל, דלקת הקיבה, דלקת בעור, עקצוץ בעור, גירוד, עור יבש, אקנה, נשירת שיער, הזעה מוגברת, הפרעה בראיה כולל טשטוש ראיה, רעש מתמשך באוזניים, עין יבשה, חבורה, דכאון, נדודי שינה, חבלות, אנורקסיה, ישנוניות, בצקת כללית, כאב במפרקים, חולשת שרירים, דלקת שרירים, כאב בחזה, כאב באזור הידיים והרגליים, צמרמורת, כאב בטן, נוקשות שרירים ומפרקים, התכווצות שרירים.בדיקות מעבדה עשויות להראות: נוזלים סביב הלב, נוזלים בריאות, הפרעות בקצב הלב, נויוטרופניה פיברילית, , דימום במערכת העיכול, רמות חומצה אוראית גבוהות בדם.תופעות לוואי שאינן נפוצות (תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000):* התקף לב, דלקת הרירית המקיפה את הלב, קצב לב לא סדיר, כאבים בחזה בשל חוסר אספקת דם ללב (אנגינה), לחץ דם נמוך ,קשיי נשימה עקב הצרות קנה, אסטמה, לחץ דם מוגבר בעורקי הריאות, דלקת של הלבלב ,כיב פפטי, דלקת בדרכי העיכול, בטן נפוחה, קרע בעור של התעלה האנאלית, קושי בבליעה, דלקת של כיס המרה, חסימה של צנרת כיס המרה, החזר קיבתי ושטי (ריפלוקס) תגובה אלרגית כולל צברים אדומים ורגישים על העור (erythema nodosum) , חרדה, בלבול, שינויים במצב רוח, דחף מיני נמוך, עילפון, רעד ,דלקת של העין שגורמת לאדמומיות או לכאב, מחלת עור המתאפיינת בכתמים אדומים, רגישים, מוגדרים היטב המלווים בהתפרצות פתאומית של חום וספירת תאי דם לבנים גבוהה (neutrophilic dermatosis) ,אובדן שמיעה, רגישות לאור ,ליקוי ראייה, הפרשה מוגברת של דמעות, שינוי בצבע העור, דלקת ברקמת השומן מתחת לעור,כיב בעור ,שלפוחיות בעור, שינוי בציפורניים, שינוי בשיער, הפרעה ביד/רגל, אי ספיקת כליות, תכיפות במתן שתן, הגדלת חזה אצל גברים, הפרעה בוסת, חולשה ואי נוחות כללית, תת פעילות בלוטת התריס, איבוד שיווי משקל בזמן הליכה, נמק העצם (osteonecrosis – פגיעה בכלי הדם המזינים את העצם, הגורמת לאובדן ולמות תאי עצם), דלקת מפרקים, , נפיחות בעור במקומות שונים בגוף, דלקת ורידית העלולה לגרום לאדמומיות, רגישות ונפיחות , דלקת של הגיד, אובדן זיכרון.בדיקות עשויות להראות: תוצאות בדיקת דם לא תקינות ותפקוד כליות לקוי הנגרם מפינוי חומרי הפסולת של הגידול (tumour lysis syndrome) , רמות נמוכות של אלבומין בדם, רמות נמוכות של לימפוציטים בדם, רמה גבוהה של כולסטרול בדם, בלוטות לימפה נפוחות, דימום במוח, אי סדירות בפעילות החשמלית של הלב, לב מוגדל, דלקת של הכבד, חלבון בשתן, עלייה באנזים קריאטין פוספוקינאז, עלייה בטרופונין, עלייה בגאמא-גלוטמיל-טרנספראז.

תופעות לוואי נדירות (תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000):הגדלה של חדר הלב הימני, דלקת של שריר הלב , מצבים שונים הנוצרים כתוצאה מחסימה של אספקת דם לשריר הלב (acute coronary syndrome), דום לב, מחלת לב כלילית, דלקת של הרקמה המכסה את הלב והריאות, קרישי דם, קרישי דם בריאות, אובדן של חומרי תזונה חיוניים כמו חלבון ממערכת עיכול , חסימת מעיים, פיסטולה בפי הטבעת, פגיעה בתפקודי כליות, סכרת, עוויתות , דלקת של עצב הראייה העלולה לגרום לאובדן מלא או חלקי של ראייה, , גוון כחלחל-סגלגל של העור, פעילות יתר של בלוטת התירס, דלקת בלוטת התריס, אטקסיה (הפרעה בקואורדינציה), קושי בהליכה, הפלה, דלקת של כלי דם בעור, צלקת פיברוטית בעור, שבץ, חוסר תפקוד נוירולוגי זמני כתוצאה מזרימת דם לקויה, שיתוק בעצב הפנים, שיטיון (דמנציה).תופעות לוואי נוספים שדווחו (בתדירות לא ידועה) כוללות: דלקת ריאות , דימומים בקיבה או במעיים העלולים לגרום למוות, חום, שלפוחיות על העור והתכייבות ממברנות ריריות. אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא. |

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב**.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.