BRISTOL-MYERS SQUIBB RESEARCH AND DEVELOPMENT

DASATINIB

SUMMARY OF THE RISK MANAGEMENT PLAN FOR SPRYCEL® (DASATINIB)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of SPRYCEL® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of SPRYCEL® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP for SPRYCEL®.

1 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for SPRYCEL (dasatinib)

This is a summary of the risk management plan (RMP) for SPRYCEL. The RMP details important risks of SPRYCEL, how these risks can be minimised, and how more information will be obtained about SPRYCEL's risks and uncertainties (missing information).

SPRYCEL's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SPRYCEL should be used.

This summary of the RMP for SPRYCEL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SPRYCEL's RMP.

1.1 The Medicine and What It Is Used For

SPRYCEL is authorised for use in adults with newly diagnosed Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukaemia (CML) in Chronic Phase (CP); adults with CP, Accelerated Phase (AP), or Blast Phase (BP) CML with resistance or intolerance to prior therapy including imatinib; and Ph+ Acute Lymphoblastic Leukaemia (ALL) and lymphoid BP CML with resistance or intolerance to prior therapy. (see SmPC for the full indication). SPRYCEL is authorised for use in paediatric patients with newly diagnosed Ph+ CML in CP, or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. It contains dasatinib as the active substance and it is given orally by tablet or powder for oral suspension (PFOS).

Further information about the evaluation of SPRYCEL’s benefits can be found in SPRYCEL’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000709/human_med_001062.jsp&mid=WC0b01ac058001d124.

1.2 Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of SPRYCEL, together with measures to minimise such risks and the proposed studies for learning more about SPRYCEL's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

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- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of SPRYCEL, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SPRYCEL is not yet available, it is listed under 'missing information' below.

1.2.1 List of Important Risks and Missing Information

Important risks of SPRYCEL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SPRYCEL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	Myelosuppression Fluid Retention Bleeding Related Events QT Prolongation PAH Pregnancy Related Malformative or Foeto/ Neonatal Toxicity Nephrotic Syndrome Thrombotic Microangiopathy
Important potential risks	Severe Hepatotoxicities Direct Cardiotoxic Effects (eg, Cardiomyopathy) Growth and development disorders and bone mineral metabolism disorders in the paediatric population Toxic Skin Reactions CYP3A4 Drug Interactions HBV Reactivation
Missing information	Carcinogenicity Paediatric data • Children < 1 year of age Reproductive and lactation data

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1.2.2 Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risks

Myelosuppression	
Evidence for linking the risk to the medicine	Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is disease phase dependent and is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily and/or dose reduction
Risk factors and risk groups	The risk of myelosuppression is dose dependent. Myelosuppression is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Other risk factors: hepatic impairment (≥ Grade 2 alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), CYP3A4 inhibitors, preexisting myelosuppression, prior imatinib treatment and chemotherapy, underlying haematologic malignancies.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8 SPRYCEL is a medicinal product subject to restricted medical prescription
Fluid Retention	
Evidence for linking the risk to the medicine	Dasatinib may cause various types of fluid retention. Fluid around the lining of the lung (pleural effusion) or heart (pericardial effusion), or fluid in the lungs (pulmonary oedema) may cause shortness of breath. Fluid in the abdomen (ascites) can cause abdominal discomfort or shortness of breath. Fluid under the skin (superficial oedema) can occur in various places in the body and may cause swelling or discomfort.
Risk factors and risk groups	Risk factors include older age, fluid retention at baseline, prior imatinib treatment, and renal impairment. While the safety profile of dasatinib in the elderly population was generally similar to that in the younger population, the incidence of pleural effusion increases with age. For example, patients aged 65 years and older are more likely to experience fluid retention events and should be monitored closely.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8.

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Important Identified Risks

Bleeding Related Events	
Evidence for linking the risk to the medicine	Bleeding has been very common in studies with dasatinib affecting more than 1 out of every 10 patients and can occur in any part of the body such as the brain, stomach or intestines. Severe and life-threatening or fatal bleeding has occurred.
Risk factors and risk groups	Patients with leukaemia, severe thrombocytopaenia, coagulation disorder,cardiovascular disorders, and patients who take medicinal products that inhibit platelet function or anticoagulants. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopaenia CNS haemorrhage is a known complication of leukaemia and, like GI haemorrhage, typically results from severe thrombocytopaenia or platelet dysfunction. GI haemorrhage is a known comorbid condition in an acutely ill population of Leukaemic patients, typically resulting from thrombocytopaenia or platelet dysfunction. Among these subjects without significant thrombocytopaenia, the frequency of haemorrhage events was similar between the dasatinib and imatinib groups (any grade: 9.4% vs 9.1%; Grade 3 to 4: 1.8% vs 1.5%). There was a trend toward more frequent "other" (defined as ear haemorrhage, epistaxis, gingival bleeding, haematoma, haematuria, haemoptysis, petechiae, and scleral haemorrhage) haemorrhage events with imatinib (dasatinib: 6.4%, imatinib: 8.1%). These data suggest that among subjects with adequate platelet counts for normal hemostasis, bleeding events were infrequent and low grade among both treatment groups.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8
QT Prolongation	
Evidence for linking the risk to the medicine	Dasatinib may increase the risk of prolongation of QTc in patients including those with hypokalaemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
Risk factors and risk groups	Patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which lead to QT prolongation, and cumulative high dose anthracycline therapy. Other risk factors include baseline QT prolongation, cardiac history (eg, CHF, bradycardia, MI), elderly, and female.

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Important Identified Risks

Risk minimisation measures	SmPC Sections 4.4 and 4.8
Pulmonary Arterial Hypertension (PAH)	
Evidence for linking the risk to the medicine	Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of dasatinib.
Risk factors and risk groups	The cumulative search through 27-Jun-2013, provided the following information on each risk group/risk factor: **Gender and age:** As with all post-marketing the reporting age and gender of patients was not reported in all cases. Gender was provided in 75 of the reported 86 cases of PAH (35 males, and 40 females). Age and gender were provided in all 39 cases of catheter confirmed PAH. In the catheter confirmed PAH group, 25 of the 39 reported cases were female. The median age of patients was slightly lower in the catheter confirmed PAH group when compared to the total group. Of note, the median age of subjects enrolled in the clinical trial program in second line therapy is 56 years. The median age of patients with catheter confirmed PAH was 53 years. **Underlying disease:** The majority of patients receiving dasatinib were being treated for CML or ALL per the licensed indications, although occasional cases of solid tumours were reported with PH from other clinical trials with dasatinib. A single literature report of PAH associated with dasatinib use in metastatic malignant melanoma is the only report of off label use and PAH. **Prior medical history:** Of the 39 subjects with catheter confirmed PAH, 5 had prior medical histories of fluid retention events (pleural effusion, generalized oedema) reported with dasatinib or prior TKI treatment before the episode of PAH. An additional 10 had significant medical history of relevant serious cardiovascular-pulmonary disease including miliary tuberculosis (TB) (2), coronary artery disease requiring coronary stenting (2), myocardial infarct (1), angina (1), hypertension (1), heavy smoking (1), femoral thrombosis (1) and chronic obstructive pulmonary disease (1). **Time to onset:** Of the 86 cases of reported PAH (catheter confirmed and otherwise), the time to onset was reported in 58 cases. The time to onset of reported PAH after the initiation of treatment with dasatinib in these 58 cases ranged from 0.06 months to 84 months (mean = 30 months).

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Important Identified Risks

	The time to onset after the initiation of treatment with dasatinib in the PAH cases confirmed by RHC ranged from 0.26 months to 75 months (mean = 29 months). The interval search (28-Jun-2013 to 27-Jun-2014) provided the following information on each risk group/risk factors: **Gender and age:** Gender was reported in 25 of the 35 cases of PAH (11 males and 14 females). Age was reported in 25 cases. In these cases, the mean age was 55.6 years (range 16-73 years). **Underlying disease**: Of the 35 cases with reported PAH, all but 2 were reported as being treated for CML or ALL per the licensed indications. In one case, the indication was not reported, and a single spontaneous report of PAH associated with dasatinib use in metastatic malignant melanoma was the only report of off label use in these cases. **Prior medical history:** Of the 35 patients with PAH, several cases had relevant pre-existing or co-morbid cardiopulmonary or connective tissue disease, including preexisting arterial hypertension (9), pre-existing cardiac valvular disease (2), atrial fibrillation (2), including 1 with cardiomegaly, scleroderma (1), chronic obstructive pulmonary disease (1), pneumonia legionella (1), smoking history (3), sleep apnoea (2), and pulmonary tuberculosis (1). **Time to onset:** Time to onset of PAH after initiation with dasatinib treatment was reported in 20 of the 35 cases. The time to onset in these cases ranged from 0.33-66 months (mean = 29.5 months).
Risk minimisation measures	SmPC Sections 4.4 and 4.8.
Pregnancy Related Malformative or Foeto/ Neonatal Toxicity	
Evidence for linking the risk to the medicine	Based on limited human data, dasatinib can cause foetal harm when administered to a pregnant woman. Adverse pharmacologic effects of dasatinib including hydrops fetalis, foetal leukopenia, and foetal thrombocytopenia have been reported with maternal exposure to dasatinib Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with dasatinib and for 30 days after the final dose.
Risk factors and risk groups	**Female Partners of Male Patients:** Seven of the 82 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception. Additionally, only 4 cases provided details on contraception use, described as double barrier contraception and condoms (2 cases each). **Female Patients:** Five of the 104 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception.

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Important Identified Risks

	Additionally, 23 cases provided details on contraception use as the following: oral contraception (9), abstinence, condoms (3 each), barrier method, unspecified contraception (2 each), and abstinence/condom, contraception via temperature measurement, intramuscular contraceptive, and "safe periods" (1 each).
Risk minimisation measures	SmPC Sections 4.4, 4.6 and 5.2
Nephrotic Syndrome	
Evidence for linking the risk to the medicine	Nephrotic syndrome is a constellation of clinical and laboratory features of renal disease. Symptoms and signs include heavy proteinuria (protein excretion greater than 3.5 g/24hours), hypoalbuminemia (less than 3 g/dL), and peripheral oedema. Although untreated or unrecognized Nephrotic Syndrome may be a serious condition, the symptoms, signs and laboratory abnormalities (peripheral oedema, proteinuria and hypoalbuminuria) are easily recognized by trained medical providers.
Risk factors and risk groups	At the time of this report there were no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.
Risk minimisation measures	SmPC Section 4.8
Thrombotic Microangiopathy	
Evidence for linking the risk to the medicine	George, JN, Nester, CM Martino et al Mittal et al Corporate Safety Database.
Risk factors and risk groups	At the time of this report, there are no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.
Risk minimisation measures	SmPC Sections 4.4 and 4.8
Severe Hepatotoxicities	
Evidence for linking the risk to the medicine	Patients treated with dasatinib may be at increased risk of developing damage to the liver. Other drugs for CML treatment like dasatinib are known to cause liver damage. Patients on dasatinib have had damage to the liver develop. Patients with advanced phase CML or Ph+ ALL are more likely to show evidence of liver damage when on dasatinib. It is unknown if the damage was caused by the treatment or the leukaemia disease itself.
Risk factors and risk groups	No risk factors have been identified for subjects developing hepatic AEs with dasatinib. Severe hepatotoxicity is more common in advanced leukaemic disease and may be confounded by the disease itself.
Risk minimisation measures	SmPC Sections 4.4, 4.8 and 5.3

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Important Identified Risks

Direct Cardiotoxic Effect (eg Cardiomyopathy)	
Evidence for linking the risk to the medicine	The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease.
Risk factors and risk groups	The incidence of CHF increases with age. CHF incidence approaches 1% in patients over 65 years of age and approximately 75% of CHF cases have hypertension. Several chemotherapy agents are associated with cardiotoxicities in other tumour types. Prior exposure to IFN-therapy or anthracyclines, pre- existing cardiac condition, and increasing age may all impact the risk of developing CHF. In CA180056 with 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, while the protocol excluded subjects with significant recent cardiac events within 3 to 6 months prior to enrolment, nearly one quarter of the subjects had some degree of cardiac comorbidity. The most common cardiac comorbidities among randomized subjects were hypertension (dasatinib 13.5%, imatinib 13.1%), hyperlipidaemia (dasatinib 8.5%, imatinib 7.3%), diabetes (dasatinib 6.9%, imatinib 5.0%), and peripheral artery disease (dasatinib 2.7%, imatinib 1.5%). Cardiac events were more than twice as likely in subjects with cardiac comorbidity at baseline compared with subjects without cardiac comorbidity at baseline in both groups.
Risk minimisation measures	SmPC Sections 4.2, 4.4, and 4.8
Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population	
Evidence for linking the risk to the medicine	Children with leukaemia who are receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments.
Risk factors and risk groups	Patients of pre-pubertal age may be at increased risk for any potential growth related effects. Paediatric patients with leukaemia or receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments. It is unknown if treatment with dasatinib in this setting will alter this risk.
Risk minimisation measures	SmPC Section 4.8

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Important Identified Risks

Toxic Skin Reactions	
Evidence for linking the risk to the medicine	Toxic skin reactions are rare diseases. The annual incidence is 1.2- 6.0 cases per million persons for Steven Johnson syndrome and 0.4 - 1.9 cases per million persons for toxic epidermal necrolysis. Infection (eg herpes simplex virus and mycoplasma pneumoniae) is the identified etiology for the majority of erythema multiforme (EM) cases. However, therapeutic drugs and immunizations have been associated with EM as well. Mild cases of EM resolve without sequelae and do not require treatment Based on the currently available information, these happen to be rare events with the use of dasatinib. Impact of the medication may be mild to very severe skin reactions. There have been 14 cases reported since the time dasatinib has been on market (Since Jun-2006) where patients experienced mild to severe form of skin reactions. Patients have been reported to recover once dasatinib was interrupted or stopped. Patients may receive fluids, electrolytes, mechanical supplementation and wound care in some cases for treatment of these skin reactions.
Risk factors and risk groups	Patient groups most at risk for SJS and TEN include the elderly, women, immunocompromised, and those with slow acetylator genotypes. A strong association between therapeutic drugs and development of cutaneous eruptions is observed in 80% of cases; however, infections and immunizations have also been implicated in some cases. TEN is the most severe form of toxic skin reaction. The female-to-male ratio for TEN is 1.5:1. TEN may occur in all age groups; however, the mean age of patients with TEN is reported to be between 46 and 63 years. Carbamazepine-induced TEN has been observed in HLA-B*1502– positive Han Chinese patients. Based on these data, the US Food and Drug Administration recommends screening for the HLA-B*1502 allele before initiating carbamazepine in patients of Asian ancestry. There is no genotype known to be associated with toxic skin reactions in dasatinib- treated patients.
Risk minimisation measures	SmPC Section 4.8
CYP3A4 Drug Interactions	
Evidence for linking the risk to the medicine	Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. CYP3A4 substrates known to have a narrow therapeutic index (eg astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib.

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Important Identified Risks

Risk factors and risk groups	Co administration with dasatinib of CYP3A4 inhibitors, inducers, or substrates.
Risk minimisation measures	SmPC Sections 4.4, 4.5, and 4.8
HBV Reactivation	
Evidence for linking the risk to the medicine	Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
Risk factors and risk groups	Patients who have positive HBV serology at baseline are at risk of reactivation of HBV infection.
Risk minimisation measures	SmPC Sections 4.4, and 4.8 Direct Healthcare Professional Communication (DHPC) issued in EU on 11-Apr-2016.

Missing Information

Carcinogenicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3
Paediatric data: Children < 1 year of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2
Reproductive and lactation data	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3

1.2.3 Post-Authorisation Development Plan

1.2.3.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation of SPRYCEL.

1.2.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for SPRYCEL.

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