IMBRUVICA® - Risk Management Plan

Summary of Activities in the Risk Management Plan (RMP) for

IMBRUVICA® (ibrutinib)

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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 minimize them.

The RMP summary of IMBRUVICA® 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 medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

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

Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of IMBRUVICA®.

Summary of Risk Management Plan for IMBRUVICA (ibrutinib)

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

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

This summary of the RMP for IMBRUVICA 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.

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

I. The Medicine and What it is Used For

IMBRUVICA is authorized for treatment of adult patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), or Waldenström's macroglobulinemia (WM) (see SmPC for the full indications). It contains ibrutinib as the active substance and it is given as 140 mg capsules or as immediate release film-coated tablets for oral administration (140, 280, 420, and 560 mg).

Further information about the evaluation of IMBRUVICA's benefits can be found in IMBRUVICA's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003791/human_med_001801.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report 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 IMBRUVICA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of IMBRUVICA are risks that need special risk management activities to further investigate or minimize 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 IMBRUVICA. 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	Hemorrhage Hepatotoxicity (including hepatic failure) Atrial fibrillation Ventricular tachyarrhythmias Hypertension Ischemic stroke
Important potential risks	Progressive multifocal leukoencephalopathy (PML) Infections (including viral reactivation) Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias) Other malignancies (excluding non-melanoma skin cancer)
Missing information	Use in patients with severe cardiac disease

II.B. Summary of Important Risks

Important Identified Risk: Hemorrhage	
Evidence for linking the risk to the medicine	Cases of hemorrhagic events in association with ibrutinib have been reported in completed clinical trials. These events, in addition to recommendations for patients requiring anticoagulants or medication that inhibits platelet function, are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Predictors include increasing age (>60 years), history of bleeding, dose of chemotherapy, baseline platelet count, poor performance and/or nutritional status, and concomitant use of antiplatelet or anticoagulant therapy, especially warfarin use in the elderly population.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Warning not to use warfarin or other vitamin K antagonists concomitantly with ibrutinib, to avoid supplements such as fish oil and vitamin E, advice on use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function, and advice on use pre- and post-surgery is provided in SmPC Section 4.4 • Warning for patients with prior unusual bruising or bleeding and advice on concomitant use of medicines that increase the risk of bleeding is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Analysis of aggregate randomized controlled clinical trial data Final report: 3rd Quarter 2022 See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Hepatotoxicity (including hepatic failure)	
Evidence for linking the risk to the medicine	A grade 4 hepatic enzyme elevation in association with ibrutinib has been observed in a healthy volunteer in a clinical trial. Hepatic failure has been identified as an adverse reaction during postmarketing experience. These events are described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Risk factors for drug-induced liver toxicity include increasing age, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic hepatitis B virus or hepatitis C virus infection, obesity, and nonalcoholic fatty liver disease. Patients taking other anti-cancer agents, anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Atrial fibrillation	
Evidence for linking the risk to the medicine	Cases of atrial fibrillation in association with ibrutinib have been reported in completed clinical trials (particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation), and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Atrial fibrillation is more common in men than women. Other risk factors for atrial fibrillation include advanced age, hypertension and other cardiac conditions, obesity and metabolic syndrome. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races. Specifically, among CLL patients, a Mayo Clinic study observed that increased risk of incident atrial fibrillation was associated with older age, male sex, valvular heart disease, and hypertension in multivariable analysis.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4

	• Recommendations regarding management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib, are provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Ventricular tachyarrhythmias	
Evidence for linking the risk to the medicine	Cases of ventricular tachyarrhythmia in association with ibrutinib have been reported in completed clinical trials. Ventricular tachyarrhythmia has been included as a postmarketing adverse reaction in the SmPC. These events are described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Ventricular tachyarrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	Hypertension has been identified as an adverse reaction associated with ibrutinib.
Risk factors and risk groups	Risk factors for hypertension include increasing age, black race, family history of hypertension, being overweight or obese, physical inactivity, tobacco use, excess salt (sodium) in diet, too little potassium and vitamin D in diet, excess alcohol use, and stress.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding blood pressure monitoring and management of patients with hypertension are provided in SmPC Section 4.4 • Advice for patients having high blood pressure is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Ischemic stroke	
Evidence for linking the risk to the medicine	Cases of ischemic stroke in association with ibrutinib have been reported in completed clinical trials. Cerebrovascular accident, transient ischemic attack, and ischemic stroke have been included as postmarketing adverse reactions in the SmPC, based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment of the signal evaluation of ischemic stroke conducted by the Marketing Authorization Holder, considering the established cardiac risks of atrial fibrillation and hypertension associated with ibrutinib administration. Although, from a direct mechanism standpoint and based on available data, causality between stroke and treatment with ibrutinib has not been established, ischemic stroke is added to the European Union Risk Management Plan as an important identified risk as requested by PRAC, in conjunction with the addition of ischemic stroke to Sections 4.4 and 4.8 of the SmPC.
Risk factors and risk groups	The most frequent causes of ischemic stroke in cancer patients are cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation, and tobacco use. Additionally, patients receiving treatment with ibrutinib are mostly elderly and most strokes occur in people aged >65 years.-

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Signs and symptoms of stroke are provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Cases of PML (within the context of a prior or concomitant immunosuppressive therapy) in association with ibrutinib have been reported in completed clinical trials and during postmarketing experience, and are also described in the current prescribing information for ibrutinib. PML has not been identified as an adverse reaction.
Risk factors and risk groups	PML is a demyelinating disorder of the central nervous system, caused by the reactivation of the commonly occurring John Cunningham virus, which remains inactive in healthy individuals, and causes disease only when the immune system has been compromised. PML usually occurs during severe immunosuppression and the most common causes are represented by HIV infection, lymphoproliferative disorders, and other forms of cancer. The use of monoclonal antibodies (eg, natalizumab, rituximab, efalizumab) in the treatment of several dysimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, has led to an increased incidence of PML. Chemotherapy and immunosuppressive therapy are considered to be the primary risk factors in addition to HIV infection. In one analysis, 3 significant risk factors for developing PML in CLL patients were identified: age (>55 years), male sex, and CD4 cell count <200 cells/μL. A retrospective, monocentric cohort study of 976 non-Hodgkin's lymphoma patients, including 517 patients who received at least one dose of rituximab, concluded that the inclusion of rituximab into standard chemotherapy regimens for non-Hodgkin's lymphoma caused a significantly higher incidence of PML cases (rate difference: 2.2 every 1,000 patient-years; 95% confidence interval: 0.1-4.3).

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • PL Section 2 • Recommendations regarding management of patients with suspected PML are provided in SmPC Section 4.4 • Signs and symptoms of PML are provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Infections (including viral reactivation)	
Evidence for linking the risk to the medicine	Cases of infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infection) in association with ibrutinib have been reported in completed clinical trials and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Predictors include increasing age (>60 years), underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, concomitant chemotherapy, absence of antibiotic prophylaxis, and poor performance and/or nutritional status.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Preventive measures and management regarding hepatitis B reactivation are provided in SmPC Section 4.4 • Warning for patients who had or have a hepatitis B infection is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	
Evidence for linking the risk to the medicine	Cases of cardiac arrhythmia in association with ibrutinib have been reported in completed clinical trials, and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Arrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 5.1 • PL Section 2 • PL Section 4 • Recommendations regarding management of patients who develop symptoms of cardiac arrhythmia are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Other malignancies (excluding non-melanoma skin cancer)	
Evidence for linking the risk to the medicine	Cases of other malignancies (including solid tumors and hematologic tumors) in association with ibrutinib have been reported in ongoing and completed clinical trials. Other malignancies has not been identified as an adverse reaction.
Risk factors and risk groups	The chance of developing a second cancer depends on a number of factors including type of primary cancer, age at diagnosis, sex, types of therapy given, environmental exposures, genetic predisposition, and health decisions. Radiation has long been associated with the development of primary cancers and, when used as treatment, imparts a risk for the development of a second cancer. Leukemia as a second primary cancer can occur following treatment with chemotherapy. Although acute myelogenous leukemia is the most common type of therapy-related leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome have also been reported. Chemotherapy-induced myeloid leukemias are relatively resistant to subsequent therapy and have a cure rate of only 10% to 20%, stressing the importance of primary prevention.

Risk minimization measures	Routine risk minimization measures: • Legal status: restricted medical prescription

Missing Information: Use in patients with severe cardiac disease	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 4 • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Recommendations regarding management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib, are provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of IMBRUVICA.

II.C.2. Other Studies in Postauthorization Development Plan

Analysis of aggregate randomized controlled clinical trial data – Additional pharmacovigilance study to further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs

Purpose of the study: To further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs

PCI-32765MCL3002 - A randomized, double-blind, placebo-controlled Phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma

Purpose of the study: Evaluate efficacy and safety of ibrutinib in combination with BR versus BR alone