# BRUKINSA® - Risk Management Plan

# Summary of Risk Management Plan (RMP) for BRUKINSA® (zanubrutinib)

Version number of current RMP: 0.2 dated 13 May 2021

Marketing Authorisation Holder: BeiGene Switzerland GmbH

Date: 11 April 2022

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 risks as well as to prevent or minimize them.

The RMP summary of BRUKINSA® 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 authorization.

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

BeiGene Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of BRUKINSA®.

# SUMMARY OF RISK MANAGEMENT PLAN FOR BRUKINSA (ZANUBRUTINIB)

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

The BRUKINSA Product Information for Professionals and Patient Information Leaflet provide essential information to healthcare professionals and patients as to how BRUKINSA should be used.

## I THE MEDICINE AND WHAT IT IS USED FOR

BRUKINSA is an anticancer medicine that contains the active substance zanubrutinib. It belongs to a class of medicines called protein kinase inhibitors. BRUKINSA works by blocking Bruton tyrosine kinase, a protein in the body that helps cancer cells grow and survive. By blocking this protein, BRUKINSA helps kill and reduce the number of cancer cells, which can slow down the worsening of the cancer.

Waldenström macroglobulinaemia is a rare, slow growing type of cancer that begins in the white blood cells. In this condition, the bone marrow produces too many abnormal white blood cells that can overcome healthy blood cells. Waldenström macroglobulinaemia, also sometimes called lymphoplasmacytic lymphoma, is classified as a type of B-cell non-Hodgkin lymphoma. It is a rare disease that affects about 4 to 5 people per 1,000,000 in Europe and < 1 in 100,000 people throughout the rest of the world. Waldenström macroglobulinaemia occurs more frequently in older adults, the average age at diagnosis being in the mid-60s. It is more common in men than women, and white people are at a higher risk than black people.

The abnormal white blood cells produce a large protein called a macroglobulin that builds up in the blood where it can impair circulation and cause complications. Some people with Waldenström macroglobulinaemia may not experience many symptoms early on when the disease is first diagnosed. However, the overproduction of the macroglobulin in Waldenström macroglobulinaemia can make the blood more viscous (ie, thick and stickier), restricting circulation and resulting in a condition called hyperviscosity, which can cause easy bruising, headaches, nose bleeds, and blurred vision.

In a main study involving 201 patients who were either untreated for Waldenström macroglobulinaemia or did not respond to or had come back after previous treatment, BRUKINSA was shown to be an effective treatment with favourable responses to treatment when compared with another medicine used to treat this condition. Furthermore, patients treated with BRUKINSA demonstrated a favourable safety and tolerability profile in patients with Waldenström macroglobulinaemia. The average treatment duration was > 18 months.

# II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of BRUKINSA, together with measures to minimise such risks and the proposed studies for learning more about BRUKINSA risks, are described below. These are risks that require special risk management activities in order to investigate them more thoroughly, to help understand how BRUKINSA can be used safely. There are 2 kinds of risks, identified and potential risks. Concerns are called identified risks when there is evidence of a link with the use of BRUKINSA. Concerns are called potential risks where this evidence is not as strong and where this needs further investigation. In addition, there is missing information that refers to concerns where information is missing or insufficient and where further evidence needs to be collected. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Patient Information Leaflet and Product Information for Professionals 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 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 minimise any risks that may be associated with its use

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and analysed regularly, including periodic assessment, so that immediate action relating to the safety of BRUKINSA can be taken if considered necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of BRUKINSA is not yet available, it is listed under 'Missing Information', below.

## II.A List of Important Risks and Missing Information

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Haemorrhage |
| Important potential risks | Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter<br>Cytopenia<br>Infections<br>Second primary malignancies<br>Drug-drug interaction<br>Teratogenicity<br>Severe cutaneous adverse reactions |
| Missing information | Safety in patients with severe hepatic impairment<br>Safety in patients with severe renal impairment/on dialysis<br>Use in patients with moderate to severe cardiac impairment<br>Long-term safety (> 2 years)<br>Safety in paediatric patients<br>Safety in pregnancy and lactation |

## II.B Summary of Important Risks

| **Important identified risk: Haemorrhage** | |
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| Evidence for linking the risk to the medicine | No apparent haemorrhage has been observed in animal studies, however, haemorrhage events have been reported relating to the use of BRUKINSA in ongoing and completed clinical studies.<br>Such events, in addition to recommendations to prescribers regarding the use of BRUKINSA in patients that are also receiving treatment with anticoagulants or medications that inhibit platelet function, are described in the Product Information for Professionals for BRUKINSA. |
| Risk factors and risk groups | Risks include advanced age, 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 minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Dosage/Administration<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Undesirable effects<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

| **Important potential risk: Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter** | |
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| Evidence for linking the risk to the medicine | Reports of atrial fibrillation have been identified in completed and ongoing clinical studies, particularly in patients with a history of cardiac disease and known cardiac risk factors (eg, hypertension, previous history of atrial fibrillation and concurrent active infections). Atrial fibrillation is described in the current prescribing information for ibrutinib. |
| Risk factors and risk groups | Atrial fibrillation is the most common heart rhythm disorder. Atrial fibrillation is more common in men than women. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races. Other lifestyle factors that predispose individuals to atrial fibrillation include a sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnoea, cardiac conditions, hypertension, and hyperlipidaemia. |
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Undesirable effects<br>Product Information for Professionals: Pharmacodynamics<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

| **Important potential risk: Cytopenia** | |
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| Evidence for linking the risk to the medicine | Reports of cytopenias (low blood counts) have been identified in completed and ongoing clinical studies of zanubrutinib in patients with B cell malignant disorders. Events of neutropenia (reduced neutrophil count), anaemia (reduced red blood cell count) and thrombocytopenia (reduced platelet counts) have been infrequently reported as serious, have had limited requirement for transfusions, and have not significantly compromised the study treatment regimen. |
| Risk factors and risk groups | Neutropenia risk factors include age ≥ 65 years and female sex, prior chemotherapy and/or radiation, pre-existing neutropenia, use of myelosuppressive agents, poor immune function, hepatic or renal dysfunction, and underlying blood malignancy. Other risk factors include comorbidities such as chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, and anaemia.<br>Thrombocytopenia risk factors include older age, advanced underlying disease, prior history of thrombocytopenia, poor performance status, and prior chemotherapy use.<br>Anaemia risk factors include haematologic malignancy, diet lacking in vitamins such as vitamin B12, folate, and iron, intestinal disorders such as Crohn's disease or coeliac disease, menstruation, pregnancy, family history of anaemia, chronic conditions such as cancer, kidney or liver failure, and other factors such as alcoholism, exposure to toxic chemicals, and autoimmune disorders. |

| **Important potential risk: Cytopenia** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Dosage/Administration<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Undesirable effects<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

| **Important potential risk: Infections** | |
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| Evidence for linking the risk to the medicine | Reported events of infections (including community-acquired infections of the gastrointestinal tract, respiratory tract, skin and soft tissues, and urogenital tract, viral reactivations, and opportunistic infections) have been reported from ongoing and completed clinical studies. |
| Risk factors and risk groups | Predictors of infection include advanced age, underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, absence of antibiotic prophylaxis, and poor performance and/or nutritional status. |
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Undesirable effects<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

| **Important potential risk: Second primary malignancies** | |
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| Evidence for linking the risk to the medicine | No treatment related second primary malignancies were identified in rat repeated-dose studies for 26 weeks and in dog repeated dose studies for 39 weeks; no mutagenicity or clastogenic toxicity was noted in the core battery of genotoxicity tests. No carcinogenicity studies were conducted. Second primary malignancies have been reported in patients participating in ongoing and completed clinical studies of BRUKINSA. |
| Risk factors and risk groups | The risk of developing a second malignancy depends on several 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. Risk factors include the immunosuppressive effects of chemotherapeutic agents and radiation used to treat haematological malignancies. There is well established scientific evidence for an association between ultraviolet radiation and skin cancer, and sunlight can also cause immunosuppression. Skin cancers were observed predominantly in white, elderly males from countries with a high known prevalence of skin cancers (eg, Australia). Second primary skin cancers were not observed in patients of Asian origin. |

| **Important potential risk: Second primary malignancies** | |
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| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Undesirable effects<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

| **Important potential risk: Drug-drug interaction** | |
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| Evidence for linking the risk to the medicine | There is potential for drug-drug interactions between BRUKINSA and other concomitant medications, particularly those with strong CYP3A inhibitors and inducers. This potential of BRUKINSA was assessed in 2 dedicated clinical drug-drug interaction studies: BGB-3111-104 and BGB-3111-108. In addition, a physiologically-based pharmacokinetics model was developed to predict the effect of moderate and mild CYP3A inhibitors and CYP3A inducers on the pharmacokinetics of BRUKINSA. |
| Risk factors and risk groups | BRUKINSA is metabolised primarily by CYP3A enzymes, and a clinical drug-drug interaction study and physiologically-based pharmacokinetics simulations show that strong/moderate CYP3A inhibitors or inducers can modulate exposure of BRUKINSA. Based on the results of the drug-drug interaction studies and understanding of exposure-response relationships, patients receiving medications that act as moderate to strong CYP3A inhibitors or as moderate to strong CYP3A inducers are at risk of drug-drug interactions. |
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Dosage/Administration (including recommended dose adjustments)<br>Product Information for Professionals: Interactions<br>Product Information for Professionals: Pharmacokinetics<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: Taking BRUKINSA with other medicines<br>Legal status: medical prescription |

| **Important potential risk: Teratogenicity** | |
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| Evidence for linking the risk to the medicine | Embryo-foetal development toxicity studies were conducted in both rats and rabbits. Malformations in the heart (2- or 3-chambered hearts at the incidence of 0.3% to 1.5%) were noted at all dose levels (in the absence of maternal toxicity) when administered orally to pregnant rats during the period of organogenesis. Administration of BRUKINSA to pregnant rabbits during the period of organogenesis resulted in postimplantation loss at the highest dose, but no teratogenicity was noted in this study. Adverse ocular lesions (eg, cataract, protruding eye) were recorded at all dose levels in a pre- and postnatal developmental toxicity study. Embryo-foetal toxicity may cause embryo-foetal harm.<br>In a fertility and early embryonic development study in rats, there was no effect on male or female fertility. Morphological abnormalities in sperm and increased postimplantation loss were noted. There were no apparent treatment related adverse pathological changes in reproductive organs in repeat-dose studies in rats or dogs, which is suggestive of a low risk of fertility impairment. |
| Risk factors and risk groups | Female subjects of child-bearing potential. |
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Warnings and precautions<br>Product Information for Professionals: Pregnancy, lactation<br>Product Information for Professionals: Reproductive toxicity<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: When is caution required when taking BRUKINSA?<br>Patient Information Leaflet: Can BRUKINSA be taken during pregnancy or breast-feeding?<br>Legal status: medical prescription |

| **Important potential risk: Severe cutaneous adverse reactions** | |
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| Evidence for linking the risk to the medicine | Nonclinical studies of BRUKINSA showed erosion/ulcer of the mouth/lips/eyelids in rats at doses of 500 mg/kg/day (approximately 34-fold higher than human exposure at the therapeutic dose), and rash, red discoloration, and thickened/scaling of the skin in dogs at doses ≥ 10 mg/kg/day (approximately 3-fold higher than human exposure at the therapeutic dose).<br>In ongoing and completed clinical studies, severe cutaneous adverse reaction events have been reported relating to the use of BRUKINSA. |
| Risk factors and risk groups | Severe cutaneous adverse reaction events may be a result of differing pathophysiology.<br>Certain human leukocyte antigen-I allotypes have been reported as key genetic risk factors for severe cutaneous adverse reactions induced by specific drugs. Soluble mediators and environmental and additional genetic factors may also participate in the pathophysiological mechanisms that shape the clinical pictures. |
| Risk minimisation measures | Routine risk minimisation measures:<br>Product Information for Professionals: Undesirable effects<br>Other routine risk minimisation measures:<br>Patient Information Leaflet: Which side effects may BRUKINSA have?<br>Legal status: medical prescription |

# II.C Postauthorisation Development Plan

## II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BRUKINSA.

## II.C.2 Other Studies in Postauthorisation Development Plan

There are no postauthorisation studies in the development plan for BRUKINSA.

Signature Page for VV-PVG-000837 v1.0

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