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 Summary of Product Characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients as to how BRUKINSA should be used.

This summary of the RMP for BRUKINSA should be read in the context of all information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report. Important new concerns or changes to the current ones will be included in updates of the BRUKINSA RMP.

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

Waldenström macroglobulinaemia (WM) 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. WM is considered a type of non-Hodgkin lymphoma (NHL), which is a rare type of blood cancer, and is sometimes called lymphoplasmacytic lymphoma. WM belongs to a group of blood cancers called NHLs that affect B lymphocytes. It is also 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. WM 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 WM may not experience many symptoms early on when the disease is first diagnosed. However, the macroglobulin in WM makes the blood more viscous, ie, thick and stickier, so that it does not flow easily. This is called hyperviscosity which can cause easy bruising, headaches, nose bleeds, and blurred vision.

In a main study involving 201 patients who had never received treatment for WM or either 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 WM. The average treatment duration was > 18 months.

Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a group of indolent (slow growing) NHL B-cell lymphomas, which account for approximately eight percent of all NHL cases. The average age at diagnosis is 60 years, and it is slightly more common in women than in men.

There are 3 types of MZL. Mucosa associated lymphoid tissue lymphoma is the most common type of MZL. Mucosa associated lymphoid tissue lymphoma does not start in the lymph nodes. It starts in the mucosa, which is a soft, moist tissue layer that protects and covers organs in different parts of the body. The second type of MZL, nodal MZL, starts within the lymph nodes. The third type of MZL, splenic MZL, starts in the spleen but can also be found in the bloodstream.

Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are malignant blood disorders in which there are an increased number of white blood cells in the lymphoid tissue. CLL and SLL are different forms of the same disorder, differing in the location of unhealthy blood cells, and are treated in the same way. In CLL/SLL, abnormal B lymphocytes (a type of white blood cell responsible for the production of antibodies to help fight infection) are produced instead of healthy white blood cells, and then accumulate over time. As the number of unhealthy blood cells grows, there is less room for healthy cells. The combination of fewer healthy cells and the fact that the CLL/SLL lymphocytes are poor at fighting infections can lead to frequent infection, anaemia, and easy bleeding. The uncontrolled build up and enlargement of lymphoid tissue can occur in various sites of the body such as the lymph nodes, spleen, bone marrow, and lungs. CLL/SLL can be slow-growing or fast-growing. The slower-growing form has an increased number of lymphocytes but a normal or slightly below normal level of red blood cells, platelets, and neutrophils in the blood. This form can remain stable for years. The faster-growing form has too many CLL/SLL cells in the blood that block normal cell production. As a result, the number of fully functioning red blood cells and platelet levels drop lower than normal. CLL/SLL is the most common type of leukaemia in adults and very rarely occurs in children. It is more common in older people, is rare in people younger than 40 and men are more likely to develop CLL/SLL than women.

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 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 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 Infections (including lower respiratory tract infections and hepatitis B reactivation) Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter
Important potential risks	Second primary malignancies (other than non-melanoma skin cancer) Second primary non-melanoma skin cancer Drug-drug interaction (DDI) with cytochrome P450, family 3, subfamily A (CYP3A) inhibitors and inducers Teratogenicity
Missing information	Safety in patients with severe hepatic impairment Safety in patients with severe renal impairment/on dialysis Long-term safety (> 2 years)

II.B Summary of Important Risks

Important Identified Risk: haemorrhage	
Evidence for linking the risk to the medicine	Haemorrhage events have been reported relating to the use of BRUKINSA in ongoing and completed clinical studies. 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 SmPC 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: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription

Important Identified Risk: infections (including lower respiratory tract infections and hepatitis B reactivation)	
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: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription

Important Identified Risk: cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter	
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. Most patients with atrial fibrillation/flutter had known risk factors in addition to age, including a history of atrial fibrillation, hypertension, pre-existing cardiovascular disease, or concurrent infection.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription

Important Potential Risk: second primary malignancies (other than non-melanoma skin cancer)	
Evidence for linking the risk to the medicine	BRUKINSA was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. No malignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted. Second primary malignancies (other than non-melanoma skin cancer) 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 that may increase the risk of second primary malignancies in patients with haematological malignancies include immune dysregulation, the immunosuppressive effects of chemotherapeutic agents and radiation therapy. In patients with CLL, proposed risk factors for second primary malignancy include environmental and occupational exposures, genetic risk factors, immune dysfunction inherent to the disease itself, and deoxyribonucleic acid damage from prior chemotherapy (Bond et al 2020), which are independent of BRUKINSA exposure. In a retrospective review of electronic medical records from the Ohio State University Comprehensive Cancer Center, the risk of second primary malignancies from a large cohort of patients with CLL who were previously treated with a Bruton tyrosine kinase inhibitor (545 ibrutinib-treated patients and 146 acalabrutinib-treated patients) between 2009 and 2017, was 2.2-fold (95% confidence interval: 1.7 to 2.9) higher than that expected in the general population (Bond et al 2020). On multivariable analysis, smoking was associated with increased second primary malignancy risk (hazard ratio 2.8 [95% confidence interval: 1.6 to 4.8]) and higher baseline cluster of differentiation (CD) 8 count was associated with lower second primary malignancy risk (hazard ratio 0.9 for 2-fold increase [95%

Important Potential Risk: second primary malignancies (other than non-melanoma skin cancer)	
	confidence interval: 0.8 to 0.9]). Together, these data indicate that CLL patients treated with Bruton tyrosine kinase inhibitors remain at increased risk for second primary malignancies.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription

Important Potential Risk: second primary non-melanoma skin cancer	
Evidence for linking the risk to the medicine	BRUKINSA was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. In vivo animal studies did not identify premalignant lesions at any site including the skin. ^{14}C-zanubrutinib demonstrated no accumulation in skin and BRUKINSA was not associated with melanocytes. The risk of phototoxicity was low in clinical studies. No malignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted. The most frequent second primary malignancy reported in BRUKINSA clinical studies was skin cancer. Skin cancers were observed predominantly in patients at high risk of developing skin cancer (white, elderly males from Australia, which has a high known prevalence of skin cancers). Second primary skin cancers were not observed in patients of Asian origin, or in any nonwhite patient, confirming that race and geographic location are the main drivers of non-melanoma skin cancer generation.
Risk factors and risk groups	An individual's risk of developing skin cancer depends on both constitutional and environmental factors. The constitutional risk factors of skin cancer include family history, red hair colour, melanocytic nevi, and sun exposure sensitivity (Gandini et al 2005), whereas solar ultraviolet radiation is a well-established environmental risk factor (Gandini et al 2005; Armstrong et al 1997). Sunlight can also cause immunosuppression (Onajin and Brewer 2012; Brin et al 2014). Skin cancer is the most common type of cancer in light-skinned populations around the world (Breitbart et al 2006), with skin cancers most frequent in Australia/New Zealand with an age adjusted standardised rate of 295.9 in 100.000, followed by Northern America (113.7), and Western Europe (52.9). Basal cell carcinoma, the most common malignancy in white people accounting for 80% to 85% of all non-melanoma skin cancers, has a higher occurrence in men than women, consistent with greater sun exposure (often occupational) (Diepgen and Mahler 2002). Albert et al (1990) describe incidence rates 16-fold greater in Caucasians than African Americans and > 10-fold than that observed in Hispanics.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription

Important Potential Risk: DDI with CYP3A inhibitors and inducers	
Evidence for linking the risk to the medicine	There is DDI potential between BRUKINSA and other concomitant medications, particularly those with strong CYP3A inhibitors and inducers. The DDI potential of BRUKINSA was assessed in 2 dedicated clinical DDI 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 DDI study and physiologically-based pharmacokinetics simulations show that strong and moderate CYP3A inhibitors or inducers can modulate exposure of BRUKINSA. Based on the results of the DDI 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 DDIs.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 5.2 Pharmacokinetic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription

Important Potential Risk: teratogenicity	
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. Embryo-foetal toxicity may cause embryo-foetal harm.
Risk factors and risk groups	Sexually active female patients of childbearing potential not practising birth control methods, or those known to be pregnant or lactating.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Preclinical safety data Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription

II.C Postauthorisation Development Plan

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

Short Name and Title:

BGB-3111-308 A Phase 3 Randomized, Open-label, Multicenter Study of Zanubrutinib (BGB-3111) Plus Anti-CD20 Antibodies Versus Lenalidomide Plus Rituximab in Patients With Relapsed/Refractory Follicular or Marginal Zone Lymphoma.

Purpose of the Study:

Rationale: To evaluate whether the addition of zanubrutinib to obinutuzumab (for patients with relapsed/refractory [R/R] follicular lymphoma [FL]) or rituximab (for patients with R/R MZL) will result in a favourable benefit-risk profile when compared with rituximab in combination with lenalidomide in patients with R/R FL or R/R MZL.

Objective: To evaluate the efficacy of zanubrutinib in combination with anti-CD20 monoclonal antibodies compared with lenalidomide plus rituximab in patients with R/R FL or R/R MZL.

II.C.2 Other Studies in Postauthorisation Development Plan

BGB-3111-LTE1

Short Name and Title:

BGB-3111-LTE1 - An Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies

Purpose of the Study:

Rationale: To evaluate the long-term safety and efficacy of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who are or were previously enrolled in a BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow-up.

Objective: To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib.

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