Summary Report of Benefit-Risk Assessment

BRUKINSA CAPSULE 80 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Zanubrutinib
Product Registrant	BeiGene Singapore Pte. Ltd.
Product Registration Number	SIN16341P
Application Route	Abridged evaluation
Date of Approval	01 October 2021

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A INTRODUCTION

Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

The active ingredient, zanubrutinib, is a small molecule inhibitor of Bruton's tyrosine kinase (BTK), a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, resulting in inhibition of BTK activity.

Brukinsa is available as a capsule containing 80 mg of zanubrutinib. Other ingredients in the capsule are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, edible black ink, gelatin, and titanium dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, zanubrutinib, is manufactured at Changzhou SynTheAll Pharmaceutical Co., Ltd., Changzhou, China. The drug product, Brukinsa Capsule 80 mg, is manufactured at Catalent CTS, LLC, Kansas City, United States.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Changzhou SynTheAll Pharmaceutical Co., Ltd. are adequate to support the approved storage condition and re-test period. The packaging is double low-density polyethylene bags, tied and placed in a fibre drum with lid. The drug substance is approved for storage at or below 30ºC with a re-test period of 24 months.

Drug product:

The capsule is manufactured using a direct blending approach, followed by encapsulation. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the

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manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted are adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is HDPE bottles with polypropylene child-resistant closure containing 120 capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of zanubrutinib for the treatment of patients with MCL was based primarily on one pivotal Phase II study (BGB-3111-206) and one supportive Phase I study (BGB-3111-AU-003).

Study BGB-3111-206 (Study 206) was a Phase II, multicentre, open-label, single-arm study that evaluated the efficacy and safety of zanubrutinib in adult patients with relapsed or refractory MCL who received at least one prior therapy for MCL. Patients received zanubrutinib 160 mg twice daily for up to 3 years or until disease progression, unacceptable toxicity, death, withdrawal of consent or study termination by the sponsor for the final analysis.

The primary efficacy endpoint was the objective response rate (ORR), defined as either a partial response (PR) or complete response (CR) as assessed by the Independent Review Committee (IRC) according to the 2014 Lugano classification. The Lugano classification is the currently widely used criteria for response evaluation for non-Hodgkin's lymphomas such as MCL and is considered appropriate for use in the study. The secondary efficacy endpoints included duration of response, progression-free survival (PFS), time to response and ORR as assessed by the investigator. Overall survival (OS) was an exploratory endpoint.

Tumour assessments were performed by positron-emission tomography (PET) and contrast-enhanced computed tomography (CT) every 12 weeks until Week 96 and every 24 weeks thereafter until progressive disease or end of study. PET-CT scans were required for confirmation of complete response (CR) for FDG-avid subjects; for non-avid patients only contrast CT were required for response assessment.

A total of 86 patients were enrolled into the study; all received at least one dose of study drug and were included in the Safety Analysis Set for all efficacy and safety analyses. As of the data cut-off date of 15 February 2019, the median duration of follow-up was 18.4 months (range 0.3 to 23.5 months). The median age of study subjects was 60.5 years (range 34 to 75 years). All patients (100.0%) were Chinese and the majority were male (77.9%). The median time since initial diagnosis was 30.1 months (range 3.1 to 102.4). The majority of patients had Stage IV disease (74.4%) and refractory disease (52.3%), and the majority were intermediate- (45.3%) or high-risk (38.4%) at baseline based on the Combined Biologic MCL International Prognostic Index (MIPI-b) score. The median number of prior therapy regimens was 2 (range 1 to 4).

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The primary analysis demonstrated an ORR by IRC of 83.7% (95% CI: 74.2, 90.8), ruling out the pre-specified null hypothesis of 40% with a one-sided p-value of <0.0001. The CR rate was 68.6% (95% CI: 57.7, 78.2). The investigator-assessed ORR was 83.7% (95% CI: 74.2, 90.8) and the investigator-assessed CR rate was 77.9% (95% CI: 67.7, 86.1).

The subgroup analyses of ORR generally showed consistently high ORR across the subgroups analysed, including in heavily pre-treated patients with ≥3 prior lines of therapy (ORR 75.9%; 95% CI: 56.5, 89.7) and patients with high-risk (ORR 72.7%; 95% CI: 54.5, 86.7), intermediate-risk (ORR 89.7%; 95% CI: 75.8, 97.1) or low-risk MIPI-b score (ORR 100.0%; 95% CI: 73.5, 100.0).

The median duration of response was 19.5 months (95% CI: 16.6, not estimable). A total of 53 patients (73.6%) achieved more than 12 months duration of response. The median time to response was 2.73 months (range 2.5 to 16.6). The median PFS was 22.1 months (95% CI: 17.4, not estimable). A total of 14 patients (16.3%) had died as of the data cut-off date. The median OS was not estimable as the data was immature as of the cut-off date. Meaningful conclusions cannot be drawn based on these time-to-event endpoints in the absence of a comparator arm.

Study BGB-3111-AU-003 (Study 003) was a Phase I/II, multicentre, open-label, dose-finding study in which 32 patients with relapsed or refractory MCL received treatment with zanubrutinib at a dose of either 160 mg twice daily or 320 mg once daily. Treatment continued until disease progression, intolerance or death, withdrawal of consent, or loss to follow-up. The median age was 70.5 years (range 42 to 86), the majority of patients were male (69%) and White (78%), and 3 patients (9%) were Asian. The MIPI risk score was low-risk in 28% of patients, intermediate-risk in 41% and high-risk in 31%. The majority of patients (59%) had received 1 prior line of therapy, 12% had received 2 prior lines, 22% received 3 prior lines and 6% received 4 prior lines of therapy.

The ORR in Study 003 was 84.4% (95% CI: 67.2%, 94.7%), with a CR rate of 25.0% (95% CI: 11.5, 43.4). The estimated median duration of response was 18.5 months (95% CI: 12.6, NE).

The results by dose showed similar ORR (85.7% vs 83.3%, respectively) in patients who received a dose of 160 mg twice daily versus 320 mg once daily, supporting the use of either of these doses as the recommended starting dose.

The difference in the CR rates between Study 206 (68.6%) and Study 003 (25.0%) could be contributed by the differences in response assessment, as PET scans were not mandated in Study 003. Nevertheless, the ORRs were consistently high at 84% in both studies and the median duration of response were also consistent (19.5 months in Study 206 and 18.5 months in Study 003).

Summary of key efficacy results

Endpoint	Study 206 (N=86)	Study 003 (N=32)
Objective response rate, n (%) (95% CI)	72 (83.7%) (74.2, 90.8)	27 (84.4%) (67.2, 94.7)
Best overall response		
Complete response	59 (68.6%)	8 (25.0%)[a]
Partial response	13 (15.1%)	19 (59.4%)
Stable disease	1 (1.2%)	2 (6.3%)
Progressive disease	6 (7.0%)	2 (6.3%)
Discontinued prior to first assessment	6 (7.0%)	0 (0.0%)

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No evidence of disease Unknown	1 (1.2%) 0 (0.0%)	0 (0.0%) 1 (3.1%)
Duration of response (months) Median (95% CI)	 19.5 (16.6, NE)	 18.5 (12.6, NE)

NE: not estimable
[a] FDG-PET scans were not required for response assessment.

The response rates and response durations observed with zanubrutinib in both clinical studies compared favourably with that documented for other agents used in the treatment of relapsed or refractory MCL, including other BTK inhibitors with reported ORRs ranging from 67-81%, CR rates ranging from 23-40% and median duration of response of at least 17.5 months.

Overall, the high and consistent ORR and durable responses observed with zanubrutinib in the two clinical studies provided adequate evidence supporting the efficacy of zanubrutinib for the treatment of adult patients with MCL who have received at least one prior therapy.

D ASSESSMENT OF CLINICAL SAFETY

The safety evaluation of zanubrutinib for the treatment of patients with MCL focused primarily on pooled safety data from Studies 206 and 003 comprising 123 patients with relapsed or refractory MCL (R/R MCL Pool). Of these 123 patients in the R/R MCL Pool, 118 patients received zanubrutinib monotherapy at the recommended starting dose of either 160 mg twice daily (N=100) or 320 mg once daily (N=18); 2 patients received zanubrutinib at a starting dose of 160 mg once daily, 2 patients received zanubrutinib 80 mg once daily and 1 patient received zanubrutinib 40 mg once daily.

In addition, safety data was provided from five zanubrutinib clinical studies (Studies 206, 003, 205, 210 and 1002) comprising 641 patients with MCL and other B-cell malignancies who were treated with various doses of zanubrutinib monotherapy and were included in the Integrated Safety Pool. Of these, 629 patients received either 160 mg twice daily (N=524) or 320 mg once daily (N=105).

The overall safety population (123 patients with relapsed or refractory MCL and 641 patients in the total safety pool) and the duration of exposure (median 17.5 months in the Total R/R MCL Pool) were considered adequate to reasonably assess the safety of zanubrutinib for the intended population.

Summary of treatment exposure

	Study 206 (N=86)	**R/R MCL Pool (N=123)**	**Integrated Safety Pool (N=641)**
Exposure (months) Mean (SD) Median Min, Max	 14.87 (7.206) 17.77 0.2, 23.5	 14.74 (7.726) 17.51 0.2, 33.9	 15.30 (10.384) 13.93 0.1, 49.7
Relative dose intensity (%) Mean (SD) Median Min, Max	 98.26 (7.152) 99.81 46.0, 107.1	 101.74 (46.427) 99.85 46.0, 604.4	 99.75 (34.206) 99.81 27.8, 673.2
Treatment duration ≥3 months ≥6 months ≥12 months ≥18 months ≥24 months	 74 (86.0%) 68 (79.1%) 61 (70.9%) 40 (46.5%) 0	 106 (86.2%) 96 (78.0%) 83 (67.5%) 54 (43.9%) 4 (3.3%)	 558 (87.1%) 505 (78.8%) 391 (61.0%) 212 (33.1%) 120 (18.7%)

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≥36 months	0	0	34 (5.3%)

Overview of adverse events (AEs)

	Study 206 (N=86)	R/R MCL Pool (N=123)	Integrated Safety Pool (N=641)
Any AE	83 (96.5%)	119 (96.7%)	627 (97.8%)
Treatment-related AE	77 (89.5%)	104 (84.6%)	507 (79.1%)
≥Grade 3 AE	36 (41.9%)	59 (48.0%)	370 (57.7%)
Serious AE	21 (24.4%)	37 (30.1%)	237 (37.0%)
AE leading to death	5 (5.8%)	8 (6.5%)	31 (4.8%)
AE leading to treatment discontinuation	8 (9.3%)	16 (13.0%)	64 (10.0%)
AE leading to dose reduction	2 (2.3%)	3 (2.4%)	29 (4.5%)
AE of special interest (AESI)	72 (83.7%)	105 (85.4%)	576 (89.9%)
≥Grade 3 AESI	30 (34.9%)	47 (38.2%)	302 (47.1%)
Serious AESI	17 (19.8%)	26 (21.1%)	158 (24.6%)

In the R/R MCL Pool, the most commonly reported AEs were rash (35.8%), upper respiratory tract infection (33.3%), neutrophil count decreased (31.7%), diarrhoea (22.8%), white blood cell count decreased (22.0%), platelet count decreased (21.1%), anaemia (15.4%), pneumonia (14.6%), bruising (14.6%), musculoskeletal pain (14.6%), constipation (13.0%), cough (13.0%), hypokalaemia (13.0%), hypertension (12.2%), haemorrhage (10.6%), and urinary tract infection (10.6%). The most commonly reported treatment-related AEs were neutrophil count decreased (30.1%), rash (21.1%), white blood cell count decreased (20.3%), and platelet count decreased (19.5%). The most commonly reported Grade 3 or higher AEs were neutrophil count decreased (13.8%) and anaemia (8.1%).

Serious AEs (SAEs) were reported in 37 (30.1%) patients. The SAEs reported in more than 2 patients were lung infection (5.7%), pneumonia (4.1%), and anaemia (2.4%). There were 16 (13.0%) patients with AEs leading to treatment discontinuation, the most frequent of which was pneumonia (3 [2.4%] patients). Overall, the incidence and types of AEs, SAEs and AEs leading to treatment discontinuation are consistent with the known safety profile of BTK inhibitors. The package insert for Brukinsa has included appropriate warnings and precautions for infections, cytopenias, bleeding, second primary malignancies, and atrial fibrillation and flutter.

There were 8 patients (6.5%) with AEs leading to death: pneumonia (2 patients), death (cause unspecified) (2 patients), cardiac failure congestive (1 patient), haemorrhage (1 patient), cerebral infarction (1 patient), and road traffic accident (1 patient). Overall, the AEs leading to death were either due to the known AEs associated with BTK inhibitors (e.g. infection, haemorrhage, cardiac AEs) or occurred in the setting of expected co-morbidities in the study population.

The AEs of special interest included cytopenias (neutropenia, thrombocytopenia, anaemia), infections and opportunistic infections, haemorrhage, cardiac AEs (atrial fibrillation and atrial flutter) and second primary malignancies, which are known and expected AEs of BTK inhibitors.

Summary of AEs of special interest

	Study 206 (N=86)	R/R MCL Pool (N=123)	Integrated Safety Pool (N=641)
Neutropenia	42 (48.8%)	47 (38.2%)	220 (34.3%)
≥Grade 3	17 (19.8%)	21 (17.1%)	141 (22.0%)
Thrombocytopenia	28 (32.6%)	32 (26.0%)	121 (18.9%)
≥Grade 3	4 (4.7%)	6 (4.9%)	44 (6.9%)
Anaemia	13 (15.1%)	19 (15.4%)	102 (15.9%)

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≥Grade 3	5 (5.8%)	10 (8.1%)	51 (8.0%)
Infections	53 (61.6%)	80 (65.0%)	451 (70.4%)
≥Grade 3	12 (14.0%)	18 (14.6%)	147 (22.9%)
Opportunistic infections	0 (0.0%)	3 (2.4%)	16 (2.5%)
≥Grade 3	0 (0.0%)	2 (1.6%)	7 (1.1%)
Haemorrhage	22 (25.6%)	42 (34.1%)	321 (50.1%)
≥Grade 3	1 (1.2%)	4 (3.3%)	14 (2.2%)
Hypertension	13 (15.1%)	16 (13.0%)	59 (9.2%)
≥Grade 3	3 (3.5%)	5 (4.1%)	23 (3.6%)
Atrial fibrillation/flutter	0 (0.0%)	2 (1.6%)	13 (2.0%)
≥Grade 3	0 (0.0%)	1 (0.8%)	4 (0.6%)
Second primary malignancies	0 (0.0%)	7 (5.7%)	60 (9.4%)
≥Grade 3	0 (0.0%)	1 (0.8%)	24 (3.7%)
Tumour lysis syndrome	0 (0.0%)	2 (1.6%)	2 (0.3%)
≥Grade 3	0 (0.0%)	2 (1.6%)	2 (0.3%)

The most common cytopenia AEs in the R/R MCL Pool included neutropenia (38.2%), followed by thrombocytopenia (26.0%) and anaemia (15.4%). Of the 47 (38.2%) patients with neutropenia, 21 patients had Grade 3 or higher events. Neutropenia was reported in the setting of concomitant infection in 14 (29.8%) patients and was managed with granulocyte colony-stimulating factor (G-CSF) in 19 (40.4%) patients. Most of these AEs (37/47 patients) resolved without treatment. The median time to first occurrence of neutropenia was 112.0 days. Of the 32 (26.0%) patients with thrombocytopenia, 6 patients had Grade 3 or higher events. Three patients were managed with platelet transfusion and 1 patient had treatment discontinuation. The median time to first occurrence of thrombocytopenia was 60.5 days. Of the 19 (15.4%) patients with anaemia, 10 patients had Grade 3 or higher events. The median time to the first occurrence of anaemia was 29.0 days. In 8 patients, the anaemia was managed with red blood cell transfusion. None of the cytopenia AEs were fatal.

Infections were the most common AEs of special interest reported in the zanubrutinib studies. In the R/R MCL Pool, infections were reported in 65.0% of patients, most frequently upper respiratory tract infection (33.3%), urinary tract infection (10.6%), viral upper respiratory tract infection (7.3%), lung infection (6.5%) and pneumonia (5.7%). Grade 3 or higher events were reported in 18 (14.6%) patients, with 5 (4.1%) patients requiring treatment discontinuation. The median time to first infection was 78.0 days. Of the 80 patients with infections, 52 (65.0%) patients received treatment with anti-infectives (antibacterials, antimycotics, antimycobacterials and antivirals). Three patients reported opportunistic infections, 2 with herpes simplex virus infections and 1 with bronchopulmonary aspergillosis. Two events were Grade 3 and none led to study treatment discontinuation or death. The package insert has included adequate warnings on serious infections and opportunistic infections (including fatal infections), including recommendations for monitoring for signs and symptoms of infection.

Haemorrhage events were reported in 34.1% of patients, the most frequent of which were petechiae/purpura/contusion (19 [15.4%] patients) and haematuria (8 [6.5%] patients). Four (3.3%) patients had events that were Grade 3 or higher, and 2 (1.6%) patients had events that led to treatment discontinuation. One (0.8%) patient had a fatal cerebral haemorrhage early in the treatment course. The median time from first dose of zanubrutinib to the first haemorrhage event was 47.0 days. Adequate warnings on serious haemorrhagic events (including fatal events) have been included in the package insert, including recommendations for monitoring of signs and symptoms of bleeding and caution against concomitant antiplatelet or anticoagulant use.

The incidence of atrial fibrillation and flutter events in the R/R MCL Pool was low (2 [1.6%] patients). One event was Grade 3 and was classified as an SAE. The second event was Grade

2 and was non-serious. In the Integrated Safety Pool, 13 (2.0%) patients reported atrial fibrillation (n=12) or flutter (n=1). Four patients had events that were SAEs (3 Grade 3, 1 Grade 2). No event led to treatment discontinuation. The median time from first dose of zanubrutinib to the first event was 62.0 days. Warnings on cardiac arrhythmias have been included in the package insert.

In the R/R MCL Pool, 7 (5.7%) patients reported second primary malignancies. These consisted of basal cell carcinomas (4 patients), squamous cell carcinoma of skin (1 patient), squamous cell carcinoma of head and neck (1 patient), skin cancer (1 patient), and malignant melanoma (1 patient). No events led to study treatment discontinuation. The median time from first dose of zanubrutinib to the occurrence of second primary malignancy was 168.0 days. Overall, the incidence of second primary malignancies in the zanubrutinib studies does not appear to be significantly increased over the expected incidence in patients with MCL. Nevertheless, warnings on second primary malignancies including skin and non-skin cancers have been included in the package insert.

Overall, the spectrum of AEs observed across the zanubrutinib clinical studies in patients with MCL and other B-cell malignancies are consistent with the known toxicity profile for the BTK inhibitor class. The safe use of zanubrutinib should be guided by the precautionary information and warnings in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Relapsed and refractory MCL is a rare, serious and life-threatening condition with an overall poor prognosis. Patients with relapsed or refractory MCL have a median survival of 1 to 2 years with limited available treatment options. There is a need for more effective treatments for patients with relapsed and refractory MCL.

The Phase II, single-arm study (Study 206) had demonstrated a high and clinically meaningful ORR by IRC of 83.7% (95% CI 74.2, 90.8) and CR rate of 68.6% (95% CI 57.7, 78.2) for zanubrutinib in subjects with relapsed or refractory MCL. Based on investigator assessment, consistent ORR (83.7%; 95% CI 74.2, 90.8) and CR rates (77.9%; 95% CI 67.7, 86.1) were observed. The responses were observed to be durable with a median duration of response of 19.5 months (95% CI 16.6, NE).

The absence of a comparator arm was a limitation of the single-arm study, which did not allow meaningful conclusions to be drawn on the magnitude of clinical benefit in terms of time-to-event endpoints such as PFS and OS. Nevertheless, the high ORR and durable responses observed with zanubrutinib provided adequate evidence of efficacy for zanubrutinib in the target patient population.

The most commonly reported AEs with zanubrutinib were rash (35.8%), upper respiratory tract infection (33.3%), neutrophil count decreased (31.7%), diarrhoea (22.8%), white blood cell count decreased (22.0%), platelet count decreased (21.1%), anaemia (15.4%), pneumonia (14.6%), bruising (14.6%), musculoskeletal pain (14.6%), constipation (13.0%), cough (13.0%), hypokalaemia (13.0%), hypertension (12.2%), haemorrhage (10.6%), and urinary tract infection (10.6%). The most commonly reported treatment-related AEs were neutrophil count decreased (30.1%), rash (21.1%), white blood cell count decreased (20.3%), and platelet count decreased (19.5%). The most commonly reported Grade 3 or higher AEs were neutrophil count decreased (13.8%) and anaemia (8.1%).

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Safety events that were considered events of clinical interest include cytopenias (neutropenia, thrombocytopenia, anaemia), infections and opportunistic infections, haemorrhage, cardiac AEs (atrial fibrillation and atrial flutter) and second primary malignancies, which are known and expected AEs of BTK inhibitors. These AEs have been adequately described in the package insert, including recommendations for monitoring and dose modifications.

Overall, based on the high response rates and durability of responses observed with zanubrutinib and taken together with the safety profile that is consistent with the known toxicity profile for BTK inhibitors, the benefit-risk profile of zanubrutinib in the treatment of adult patients with MCL who have received at least one prior therapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Brukinsa for the treatment of adult patients with MCL who have received at least one prior therapy was deemed favourable and approval of the product registration was granted on 01 October 2021.

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APPROVED PACKAGE INSERT AT REGISTRATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of BRUKINSA is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

BRUKINSA can be taken with or without food. Advise patients to swallow capsules whole with water. Advise patients not to open, break, or chew the capsules. If a dose of BRUKINSA is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day.

2.2 Dosage Modification for Use in Hepatic Impairment

The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Dosage Modifications for Drug Interactions

Recommended dose modifications of BRUKINSA for drug interactions are provided in Table 1 *[see Drug Interactions (7.1)]*.

Table 1: Dose Modifications for Use With CYP3A Inhibitors or Inducers

Co-administered Drug	Recommended BRUKINSA Dose
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Moderate or strong CYP3A inducer	Avoid concomitant use.

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA *[see Dosage and Administration (2.1, 2.2) and Drug Interactions (7.1)]*.

2.4 Dosage Modifications for Adverse Reactions

Recommended dose modifications of BRUKINSA for Grade 3 or higher adverse reactions are provided in Table 2:

Table 2: Recommended Dose Modification for Adverse Reaction

Event	**Adverse Reaction Occurrence**	**Dose Modification** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Grade 3 or higher non-hematological toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	First	Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily
	Second	Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily
	Third	Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: Resume at 80 mg once daily
	Fourth	Discontinue BRUKINSA

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.

3 DOSAGE FORMS AND STRENGTHS

Capsules: Each 80 mg capsule is a size 0, white to off-white opaque capsule marked with "ZANU 80" in black ink.

4 CONTRAINDICATIONS

Hypersensitivity to zanubrutinib or to any of the excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than

those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count $\geq$ 75 x 10^9/L and an absolute neutrophil count $\geq$ 1 x 10^9/L

independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CLcr ≥ 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%), and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection ¶	39	0
	Pneumonia §	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash ‖	36	0
	Bruising *	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Vascular disorders	Hypertension	12	3.4
	Hemorrhage †	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis
† Hemorrhage includes all related terms containing hemorrhage, hematoma
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis
§ Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral
‖ Rash includes all related terms containing rash
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis †	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

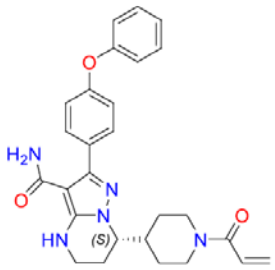
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

BRUKINSA (zanubrutinib) is a Bruton's tyrosine kinase (BTK) inhibitor. The empirical formula of zanubrutinib is $C_{27}H_{29}N_5O_3$ and the chemical name is (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide. Zanubrutinib is a white to off-white powder, with a pH of 7.8 in saturated solution. The aqueous solubility of zanubrutinib is pH dependent, from very slightly soluble to practically insoluble.

The molecular weight of zanubrutinib is 471.55 Daltons.

Zanubrutinib has the following structure:



Each BRUKINSA capsule for oral administration contains 80 mg zanubrutinib and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell contains edible black ink, gelatin, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanubrutinib is a small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

12.2 Pharmacodynamics

BTK Occupancy in PBMCs and Lymph Nodes

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over 24 hours at a total daily dose of 320 mg in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94% to 100% following the approved recommended dosage.

Cardiac Electrophysiology

At the approved recommended doses (160 mg twice daily or 320 mg once daily), there were no clinically relevant effects on the QTc interval. The effect of BRUKINSA on the QTc interval above the therapeutic exposure has not been evaluated.

12.3 Pharmacokinetics

Zanubrutinib maximum plasma concentration (C_{max}) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,295 (37%) ng·h/mL following 160 mg twice daily and 2,180 (41%) ng·h/mL following 320 mg once daily. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 314 (46%) ng/mL following 160 mg twice daily and 543 (51%) ng/mL following 320 mg once daily.

Absorption

The median t_{max} of zanubrutinib is 2 hours.

Effect of Food

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution

The geometric mean (%CV) apparent steady-state volume of distribution of zanubrutinib is 881 (95%) L. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Elimination

The mean half-life ($t_{½}$) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib is 182 (37%) L/h.

Metabolism

Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Excretion

Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (less than 1% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of zanubrutinib were observed based on age (19 to 90 years), sex, race (Asian, Caucasian, and Other), body weight (36 to 140 kg), or mild or moderate renal impairment (creatinine clearance [CL cr] ≥ 30 mL/min as estimated by Cockcroft-Gault). The effect of severe renal impairment (CLcr < 30 mL/min) and dialysis on zanubrutinib pharmacokinetics is unknown.

Hepatic Impairment

The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child-Pugh class A), by 21% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child-Pugh class A), by 43% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 194% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

CYP3A Inhibitors: Co-administration of multiple doses of CYP3A inhibitors increases zanubrutinib C_{max} and AUC (Table 6).

Table 6: Observed or Predicted Increase in Zanubrutinib Exposure After Co-Administration of CYP3A Inhibitors

Co-administered CYP3A Inhibitor	**Increase in Zanubrutinib C_{max}**	**Increase in Zanubrutinib AUC**
	Observed	
Itraconazole (200 mg once daily)	157%	278%
	Predicted	

Clarithromycin (250 mg twice daily)	175%	183%
Diltiazem (60 mg three times daily)	151%	157%
Erythromycin (500 mg four times daily)	284%	317%
Fluconazole (200 mg once daily)	179%	177%
Fluconazole (400 mg once daily)	270%	284%

CYP3A Inducers: Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92% and AUC by 93%.

Co-administration of multiple doses of efavirenz (moderate CYP3A inducer) is predicted to decrease zanubrutinib C_{max} by 58% and AUC by 60%.

CYP3A Substrates: Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%.

CYP2C19 Substrates: Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%.

Other CYP Substrates: No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics or predicted with rosiglitazone (CYP2C8 substrate) pharmacokinetics when co-administered with zanubrutinib.

Transporter Systems: Co-administration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34% and AUC by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when co-administered with zanubrutinib.

Gastric Acid Reducing Agents: No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

In Vitro Studies

CYP Enzymes: Zanubrutinib is an inducer of CYP2B6.

Transporter Systems: Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with zanubrutinib.

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats.

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 10 times the human recommended dose, based on body surface area.

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The efficacy of BRUKINSA was assessed in BGB-3111-206 [NCT03206970], a Phase 2, open-label, multicenter, single-arm trial of 86 previously treated patients with MCL who had received at least one prior therapy. BRUKINSA was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.

The median age of patients was 60.5 years (range: 34 to 75) and the majority were male (78%). The median time since diagnosis to study entry was 30 months (range: 3 to 102) and the median number of prior therapies was 2 (range: 1 to 4). The most common prior regimens were CHOP-based (91%) followed by rituximab-based (74%). The majority of patients had extranodal involvement (71%) and refractory disease (52%). Blastoid variant of MCL was present in 14% of patients. The MIPI score was low in 58%, intermediate in 29%, and high risk in 13%.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003 [NCT02343120], a Phase 1/2, open-label, dose-escalation, global, multicenter, single-arm trial of B-cell malignancies including 32 previously treated MCL patients treated with BRUKINSA. BRUKINSA was given orally at doses of 160 mg twice daily or 320 mg daily. The median age of patients with previously treated MCL was 70 years (range: 42 to 86), and 38% of patients were ≥ 75 years old. Most patients were male (69%) and Caucasian (78%). The MIPI score was low in 28%, intermediate in 41%, and high risk in 31%.

Tumor response was according to the 2014 Lugano Classification for both studies, and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee.

Table 7: Efficacy Results in Patients with MCL by Independent Review Committee

	Study BGB-3111-206 (N=86)	**Study BGB-3111-AU-003 (N=32)**
ORR (95% CI)	84% (74, 91)	84% (67, 95)
CR	59%	22%*
PR	24%	62%
Median DoR in months (95% CI)	19.5 (16.6, NE)	18.5 (12.6, NE)

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable
* FDG-PET scans were not required for response assessment

15 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HDPE bottles with a child-resistant polypropylene closure. Each carton contains one bottle of 120s.

Storage

Store below 30°C

16 MARKETING AUTHORISATION HOLDER

BeiGene Singapore Pte Ltd
38 Beach Road #29-11
Singapore 189767

17 DATE OF REVISION OF TEXT

September 2021