HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRUKINSA safely and effectively. See full prescribing information for BRUKINSA.

BRUKINSA® (zanubrutinib) capsules, for oral use
Initial U.S. Approval: 2019

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	8/2021
Dosage and Administration (2)	8/2021
Warnings and Precautions (5)	8/2021

---------- INDICATIONS AND USAGE ----------

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1.1)

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- Waldenström's macroglobulinemia (WM). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- Recommended dosage: 160 mg orally twice daily or 320 mg orally once daily; swallow whole with water and with or without food. (2.1)
- Reduce BRUKINSA dose in patients with severe hepatic impairment. (2.2, 8.7)
- Advise patients not to open, break, or chew capsules. (2.1)
- Manage toxicity using treatment interruption, dose reduction, or discontinuation. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Capsules: 80 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hemorrhage: Monitor for bleeding and manage appropriately. (5.1)
- Infections: Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed. (5.2)
- Cytopenias: Monitor complete blood counts during treatment. (5.3)
- Second Primary Malignancies: Other malignancies have occurred in patients including skin cancers. Advise patients to use sun protection. (5.4)
- Cardiac Arrhythmias: Monitor for atrial fibrillation and atrial flutter and manage appropriately. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy. (5.6)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions, including laboratory abnormalities, (≥ 20%) are neutrophil count decreased, upper respiratory tract infection, platelet count decreased, rash, hemorrhage, musculoskeletal pain, hemoglobin decreased, bruising, diarrhea, pneumonia, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BeiGene at 1-877-828-5596 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- CYP3A Inhibitors: Modify BRUKINSA dose with moderate or strong CYP3A inhibitors as described. (2.3, 7.1)
- CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage 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 dosage 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 dosage modifications of BRUKINSA for drug interactions are provided in *[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

Co-administered Drug	Recommended BRUKINSA Dose
	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 dosage modifications of BRUKINSA for Grade 3 or higher adverse reactions are provided in Table 2:

Table 2: Recommended Dosage Modification for Adverse Reaction

Event	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities *[see Warnings and Precautions (5.3)]*		
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 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 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 Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue BRUKINSA
Non-hematological toxicities *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*		
Grade 3 or 4 non-hematological toxicities *	First	Interrupt BRUKINSA Once toxicity has resolved 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 Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.

Event	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities *[see Warnings and Precautions (5.3)]*		
	Third	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue BRUKINSA

* Evaluate the benefit-risk before resuming treatment for a Grade 4 non-hematological toxicity.
^ Evaluate the benefit-risk before resuming treatment at the same dose for Grade 4 non-hematological toxicity.

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

None.

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 hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 3.0% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*.

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 28% 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 *[see Adverse Reactions (6.1)]*.

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 (28%), thrombocytopenia (11%), and anemia (7%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 4% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (4%), melanoma (1.4%), and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 2.8% 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 of atrial fibrillation and atrial flutter were reported in 0.8% of patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate *[see Dosage and Administration (2.4)]*.

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 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 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 in seven clinical trials, administered as a single agent at 160 mg twice daily in 662 patients, in patients with hematologic malignancies in clinical trials at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily (0.125 to 0.5 times the recommended dosage) in 12 patients. Among 779 patients receiving BRUKINSA, 74% were exposed for at least 1 year, 55% were exposed for at least 2 years, and 16% were exposed for at least 3 years.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in >/= 20% of patients who received BRUKINSA were neutrophil count decreased (56%), upper respiratory tract infection (49%), platelet count decreased (44%), rash (35%), hemorrhage (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), bruising (25%), diarrhea (23%), pneumonia (22%), and cough (21%).

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 ≥ 75 x 10^9/L and an absolute neutrophil count ≥ 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
Vascular disorders	Hypertension	12	3.4
	Hemorrhage †	11	3.4^
Musculoskeletal and	Musculoskeletal pain ‡	14	3.4

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
connective tissue disorders			
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.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (*MYD88^{MUT}*) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a

non-randomized arm, Cohort 2, with 26 wild type MYD88 (*MYD88^{WT}*) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male and 96% were White, and 4% were not-reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in >2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%), and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in > 2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient) and neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in > 2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia, and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in >2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in > 2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥ 10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection ¶	44	0	40	2
	Pneumonia §	12	4	26	10
	Urinary tract infection	11	0	13	2

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders and administration site conditions	Fatigue [#]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising *	20	0	34	0
	Rash	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ‡	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage †	42	4	43	9
	Hypertension	14	9	19	14

[*] Bruising includes all related terms containing "bruise," "contusion," or "ecchymosis."

[†] Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage and subarachnoid hemorrhage.

[#] Fatigue includes asthenia, fatigue, lethargy.

[‡] Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis and musculoskeletal discomfort.

[§] Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.

‖ Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatosis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, and skin toxicity.
¶ Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter, and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities* (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[1]		Ibrutinib[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry Abnormalities				
Bilirubin increased	12	1.0	33	1.0
Calcium decreased	27	2.0	26	0
Creatinine increased	31	1.0	21	1.0
Glucose increased	45	2.3	33	2.3
Potassium increased	24	2.0	12	0
Urate increased	16	3.2	34	6
Phosphate decreased	20	3.1	18	0

* Based on laboratory measurements.
[1] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 7: 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 two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 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 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 779 patients in clinical studies with BRUKINSA, 52% were ≥ 65 years of age, while 20% 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, moderate, or severe renal impairment (CLcr ≥ 15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

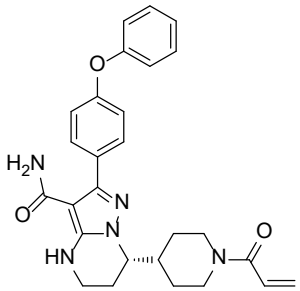
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic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

11 DESCRIPTION

BRUKINSA (zanubrutinib) is a kinase 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 Bruton's tyrosine kinase (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 2,099 (42%) ng·h/mL following 160 mg twice daily and 1,917 (59%) ng·h/mL following 320 mg once daily. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 295 (55%) ng/mL following 160 mg twice daily and 537 (55%) 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 volume of distribution (Vz/F) of zanubrutinib is 537 (73%) 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 128 (58%) 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 144 kg), or mild, moderate, or severe renal impairment (creatinine clearance [CLcr] ≥ 15 mL/min as estimated by Cockcroft-Gault). The effect of 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 8).

Table 8: 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 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 and CYP2C8.

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 9: 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.

14.2 Waldenström's Macroglobulinemia

The efficacy of BRUKINSA was evaluated in ASPEN [NCT03053440], a randomized, active control, open-label trial, comparing BRUKINSA and ibrutinib in patients with MYD88 L265P mutation (*MYD88*^{MUT}) WM. Patients in Cohort 1 (n=201) were randomized 1:1 to receive BRUKINSA 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (0 versus 1-3 versus > 3) and CXCR4 status (presence or absence of a WHIM-like mutation as measured by Sanger assay).

The major efficacy outcome was the response rate defined as PR or better as assessed by IRC based on standard consensus response criteria from the International Workshop on Waldenström's Macroglobulinemia (IWWM)-6 criteria. An additional efficacy outcome measure was duration of response (DOR).

The median age was 70 years (range: 38 to 90) and 68% were male. Of those enrolled, 2% were Asian, 91% were White and 7% were of unknown race. ECOG performance status of 0 or 1 was present in 93% patients at baseline and 7% had a baseline ECOG performance status of 2. A total of 82% had relapsed/refractory disease with 85% having received prior alkylating agents and 91% prior anti-CD20 therapy. The median number of prior therapies in those with relapsed/refractory disease was 1 (range: 1 to 8). A total of 91 (45%) patients had International Prognostic Scoring System (IPSS) high WM.

The study did not meet statistical significance for the pre-specified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN.

Table 10 shows the response rates in ASPEN based on IRC assessment.

Table 10: Response Rate and Duration of Response Based on IRC Assessment in ASPEN

	Standard IWWM-6*		Modified IWWM-6#	
Response Category	**BRUKINSA (N=102)**	**Ibrutinib (N=99)**	**BRUKINSA (N=102)**	**Ibrutinib (N=99)**
Response rate (CR+VGPR+PR), (%)	79 (77.5)	77 (77.8)	79 (77.5)	77 (77.8)
95% CI (%)[a]	(68.1, 85.1)	(68.3, 85.5)	(68.1, 85.1)	(68.3, 85.5)
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very Good Partial Response (VGPR)	16 (15.7)	7 (7.1)	29 (28.4)	19 (19.2)
Partial Response (PR), (%)	63 (61.8)	70 (70.7)	50 (49.0)	58 (58.6)
Duration of response (DOR), Event-free at 12 months (95% CI)[b]	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)

[a] 2-sided Clopper-Pearson 95% confidence interval.
[b] Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[*] IWWM-6 criteria (Owen et al, 2013) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed.
[#] Modified IWWM-6 criteria (Treon, 2015) requires a reduction in EMD if present at baseline for VGPR to be assessed.

ASPEN Cohort 2

Cohort 2 enrolled patients with MYD88 wildtype (*MYD88*^{WT}) or MYD88 mutation unknown WM (N = 26 and 2, respectively) and received BRUKINSA 160 mg twice daily. The median age was 72 years (range: 39 to 87) with 43% > 75 years, 50% were male, 96% were White and 4% were not reported (unknown race). 86% patients had a baseline ECOG performance status 0 or 1 and 14% had a baseline performance status of 2. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease.

In Cohort 2, response (CR+VGPR+PR) as assessed by IRC using IWWM-6 or modified IWWM-6 was seen in 50% (13 out of 26 response evaluable patients; 95% CI: 29.9, 70.1).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Package Size	Content	NDC Number
120-count	Bottle with a child-resistant cap containing 120 capsules 80 mg, white to off-white opaque capsule, marked with "ZANU 80" in black ink	72579-011-02

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that BRUKINSA may need to be interrupted for major surgeries or procedures *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.2)]*.

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with BRUKINSA *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with BRUKINSA, including skin cancer. Advise patients to use sun protection and have monitoring for development of other cancers *[see Warnings and Precautions (5.4)]*.

Cardiac Arrhythmias

Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 week after the last dose of BRUKINSA *[see Warnings and Precautions (5.6)]*.Advise males with female sexual partners of reproductive potential to use effective contraception during BRUKINSA treatment and for 1 week after the last dose of BRUKINSA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with BRUKINSA and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Administration Instructions

BRUKINSA may be taken with or without food. Advise patients that BRUKINSA capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of BRUKINSA, they may still take it as soon as possible on the same day with a return to the normal schedule the following day *[see Dosage and Administration (2.1)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7)]*.

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