

## Physician's Prescribing Information

### 1. Name of the Medicinal Product BRUKINSA

### 2. Qualitative and Quantitative Composition

Each capsule contains 80 mg Zanubrutinib  
For full list of excipients, see section 6.1

### 3. Pharmaceutical Form

Capsules

### 4. Therapeutic Indication

BRUKINSA is indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Waldenström's macroglobulinemia (WM).

## 5. DOSAGE AND ADMINISTRATION

### 5.1 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.

### 5.2 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 (11.7)* and *Clinical Pharmacology (13.3)*].

### 5.3 Dosage Modifications for Drug Interactions

Recommended dosage modifications of BRUKINSA for drug interactions are provided in [Table 1](#) [see *Drug Interactions (10.1)*].

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

Co-administered Drug	Recommended BRUKINSA Dose
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Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions [see <i>Dosage and Administration (5.4)</i> ].
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions [see <i>Dosage and Administration (5.4)</i> ].
Moderate or strong CYP3A inducer	Avoid concomitant use.

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA [see *Dosage and Administration (5.1, 5.2)* and *Drug Interactions (10.1)*].

## 5.4 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 Dosage Modification for Adverse Reaction

Event	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
<b>Hematological toxicities</b> [see <i>Warnings and Precautions (5.3)</i> ]		
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
<b>Non-hematological toxicities</b> [see <i>Warnings and Precautions (8.5)</i> and <i>Adverse Reactions (9.1)</i> ]		
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 <sup>^</sup>

Event	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
<b>Hematological toxicities</b> [see <i>Warnings and Precautions (5.3)</i> ]		
	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

\*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.

## 6. 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.

6.1. List of Excipients: Microcrystalline cellulose, Croscarmellose sodium, Sodium lauryl sulphate, Colloidal silicon dioxide, Magnesium stearate  
Capsule Shell : Gelatin ,Titanium Dioxide. Imprinting Ink(traces)

## 7. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *section 6.1*.

## 8. WARNINGS AND PRECAUTIONS

### 8.1 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 (9.1)*].

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.

### 8.2 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 (9.1)*]. 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.

### 8.3 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 (9.1)*]. 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 (5.4)*]. Treat using growth factor or transfusions, as needed.

### 8.4 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

### 8.5 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 (9.1)*]. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate [see *Dosage and Administration (5.4)*].

### 8.6 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 (11.1)*].

## 9 ADVERSE REACTIONS

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

- Hemorrhage [see *Warnings and Precautions (8.1)*]
- Infections [see *Warnings and Precautions (8.2)*]
- Cytopenias [see *Warnings and Precautions (8.3)*]
- Second Primary Malignancies [see *Warnings and Precautions (8.4)*]
- Cardiac Arrhythmias [see *Warnings and Precautions (8.5)*]

### 9.1 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  $\geq 20\%$  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 (15.1)*]. 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  $\geq 75 \times 10^9/L$  and an absolute neutrophil count  $\geq 1 \times 10^9/L$  independent of growth factor support, hepatic enzymes  $\leq 2.5 \times$  upper limit of normal, total bilirubin  $\leq 1.5 \times$  ULN. The BGB-3111-AU-003 trial required a platelet count  $\geq 50 \times 10^9/L$  and an absolute neutrophil count  $\geq 1 \times 10^9/L$  independent of growth factor support, hepatic enzymes  $\leq 3 \times$  upper limit of normal, total bilirubin  $\leq 1.5 \times$  ULN. Both trials required a CLcr  $\geq 30$  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 <sup>^</sup>
	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  $\geq$  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
<b>Chemistry abnormalities</b>		
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<sup>MUT</sup>*) 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<sup>WT</sup>*) WM patients and 2 patients with unknown MYD88 status [see [Clinical Studies \(15.2\)](#)].

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, 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), 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 1: 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

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades	Grade 3 or 4 (%)	All Grades	Grade 3 or 4 (%)
		(%)		(%)	
	Urinary tract infection	11	0	13	2
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 <sup>†</sup>	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, photodermatitis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, 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 2: Select Laboratory Abnormalities\* (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1**

Laboratory Abnormality	BRUKINSA <sup>1</sup>		Ibrutinib <sup>1</sup>	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Hematologic Abnormalities</b>				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
<b>Chemistry Abnormalities</b>				
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.

<sup>1</sup> 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.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

## **10 DRUG INTERACTIONS**

### **10.1 Effect of Other Drugs on BRUKINSA**

**Table 7: Drug Interactions that Affect Zanubrutinib**

<b>Moderate and Strong CYP3A Inhibitors</b>
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<i>Clinical Impact</i>	<ul style="list-style-type: none"> <li>• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C<sub>max</sub> and AUC [see <i>Clinical Pharmacology (13.3)</i>] which may increase the risk of BRUKINSA toxicities.</li> </ul>
<i>Prevention or management</i>	<ul style="list-style-type: none"> <li>• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see <i>Dosage and Administration (5.3)</i>].</li> </ul>
<b>Moderate and Strong CYP3A Inducers</b>	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> <li>• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C<sub>max</sub> and AUC [see <i>Clinical Pharmacology (13.3)</i>] which may reduce BRUKINSA efficacy.</li> </ul>
<i>Prevention or management</i>	<ul style="list-style-type: none"> <li>• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers [see <i>Dosage and Administration (5.3)</i>].</li> </ul>

## 11 USE IN SPECIFIC POPULATIONS

### 11.1 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.

## 11.2 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.

## 11.3 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 (11.1)*]. 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.

## 11.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

## 11.5 Geriatric Use

Of the 779 patients in clinical studies with BRUKINSA, 52% were  $\geq 65$  years of age, while 20% were  $\geq 75$  years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

## 11.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment ( $\text{CLcr} \geq 15$  mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis [see *Clinical Pharmacology (13.3)*].

## 11.7 Hepatic Impairment

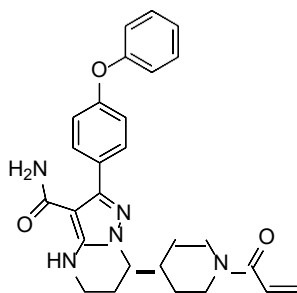
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment [see *Dosage and Administration (5.2)*]. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment [see *Clinical Pharmacology (13.3)*].

## 12 DESCRIPTION

BRUKINSA (zanubrutinib) is a kinase inhibitor. The empirical formula of zanubrutinib is  $\text{C}_{27}\text{H}_{29}\text{N}_5\text{O}_3$  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.

## 13 CLINICAL PHARMACOLOGY

### 13.1 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.

### 13.2 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.

### 13.3 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 ( $V_z/F$ ) 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 ( $t_{1/2}$ ) 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 [CL<sub>cr</sub>] ≥ 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<sub>max</sub> and AUC ([Table 8](#)).

**Table 8: Observed or Predicted Increase in Zanubrutinib Exposure After Co-Administration of CYP3A Inhibitors**

<b>Co-administered CYP3A Inhibitor</b>	<b>Increase in Zanubrutinib C<sub>max</sub></b>	<b>Increase in Zanubrutinib AUC</b>
	<i>Observed</i>	
Itraconazole (200 mg once daily)	157%	278%
	<i>Predicted</i>	

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, H<sub>2</sub>-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.

## 14 NONCLINICAL TOXICOLOGY

### 14.1 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.

## 15 CLINICAL STUDIES

### 15.1 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**

	<b>Study BGB-3111-206 (N=86)</b>	<b>Study BGB-3111-AU-003 (N=32)</b>
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

## 15.2 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<sup>MUT</sup>*) 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

Response Category	Standard IWWM-6*		Modified IWWM-6#	
	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 (%) <sup>a</sup>	(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) <sup>b</sup>	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)

<sup>a</sup> 2-sided Clopper-Pearson 95% confidence interval.

<sup>b</sup> 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<sup>WT</sup>*) 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
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

### Storage

Store below 25°C

Shelf life

The expiry date of the product is indicated on the packaging materials.

**17. MANUFACTURER**

BeiGene USA, Inc.  
San Mateo, CA 94403

**18. LICENSE HOLDER**

Medison Pharma Ltd.  
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**19. REGISTRATION NUMBER**

**166-56-36452-99**

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