



# BRUKINSA DOSING AND ADMINISTRATION GUIDE

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## **INDICATION**

BRUKINSA™ (zanubrutinib) is a kinase inhibitor 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**Please see Important Safety Information on pages 10–11, and accompanying full Prescribing Information.**

## BRUKINSA RECOMMENDED DOSING

The recommended dose is **320 mg** daily until disease progression or unacceptable toxicity<sup>1</sup>

BRUKINSA can be taken as **160 mg twice daily** or **320 mg once daily**<sup>1</sup>

## ADMINISTRATION<sup>1</sup>

- Can be taken with or without food
- Should be swallowed 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

Please see Important Safety Information on pages 10-11, and accompanying full Prescribing Information.

## HOW SUPPLIED

Strength <sup>1</sup>	Package Size <sup>1</sup>	NDC Number <sup>1</sup>
80 mg	120 capsules	72579-011-02

## STORAGE AND HANDLING

- Store at room temperature from 20°C to 25°C (68°F to 77°F)<sup>1</sup>
- Excursions permitted from 15°C to 30°C (59°F to 86°F)<sup>1</sup>



## RECOMMENDED DOSE MODIFICATION FOR USE IN HEPATIC IMPAIRMENT

The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily

## RECOMMENDED DOSE MODIFICATION FOR ≥GRADE 3 ADVERSE REACTIONS

### Event<sup>1</sup>

- 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)

**Dose Modification** (starting dose: 160 mg twice daily or 320 mg once daily)<sup>1</sup>

<b>1ST OCCURRENCE</b>	<b>Interrupt BRUKINSA</b> Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 160 mg twice daily or 320 mg once daily
<b>2ND OCCURRENCE</b>	<b>Interrupt BRUKINSA</b> Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 80 mg twice daily or 160 mg once daily
<b>3RD OCCURRENCE</b>	<b>Interrupt BRUKINSA</b> Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 80 mg once daily
<b>4TH OCCURRENCE</b>	<b>Discontinue BRUKINSA</b>

## RECOMMENDED DOSE MODIFICATION FOR USE WITH CYP3A INHIBITORS OR INDUCERS

Coadministered Drug <sup>1</sup>	Recommended Dose <sup>1</sup>
<b>Strong CYP3A inhibitor</b>	80 mg once daily Interrupt dose as recommended for adverse reactions
<b>Moderate CYP3A inhibitor</b>	80 mg twice daily Interrupt dose as recommended for adverse reactions
<b>Moderate or strong CYP3A inducer</b>	Avoid concomitant use

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA.

Please see Important Safety Information on pages 10–11, and accompanying full Prescribing Information.



## DRUG INTERACTIONS

Drugs <sup>1</sup>	Interaction <sup>1</sup>
<b>Moderate and Strong CYP3A Inhibitors</b>	Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib $C_{max}$ and AUC which may increase the risk of BRUKINSA toxicities.
<b>Moderate and Strong CYP3A Inducers</b>	Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib $C_{max}$ and AUC which may reduce BRUKINSA efficacy.
<b>Gastric Acid Reducing Agents</b>	No clinically significant differences in zanubrutinib pharmacokinetics (PK) were observed when coadministered with gastric acid reducing agents (proton pump inhibitors, H <sub>2</sub> -receptor antagonists).
<b>CYP Substrates</b>	Coadministration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) and omeprazole (CYP2C19 substrate) $C_{max}$ and AUC.  No clinically significant differences were observed with warfarin (CYP2C9 substrate) PK or predicted with rosiglitazone (CYP2C8 substrate) PK when coadministered with zanubrutinib.
<b>Transporter Systems</b>	Coadministration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) $C_{max}$ and AUC. No clinically significant differences in the PK of rosuvastatin (BCRP substrate) were observed when coadministered with zanubrutinib.

## SPECIFIC POPULATIONS

### LACTATION<sup>1</sup>

- Advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose

### FEMALES AND MALES OF REPRODUCTIVE POTENTIAL<sup>1</sup>

- Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy
- Females: 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: Avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA

### PEDIATRICS<sup>1</sup>

- Safety and effectiveness in pediatric patients have not been established

### GERIATRICS<sup>1</sup>

- No overall differences in safety or effectiveness were observed between younger and older patients

### RENAL IMPAIRMENT<sup>1</sup>

- No dosage modification is recommended in patients with mild to moderate renal impairment
- Monitor for BRUKINSA adverse reactions in patients with severe renal impairment or on dialysis

### HEPATIC IMPAIRMENT<sup>1</sup>

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment. 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.

Please see Important Safety Information on pages 10–11, and accompanying full Prescribing Information.



## BRUKINSA WAS EVALUATED GLOBALLY IN 2 CLINICAL TRIALS

### STUDY 206

Study BGB-3111-206 (Study 206) was a Phase 2 open-label, multicenter, single-arm trial of 86 previously treated MCL patients enrolled in China who had received at least 1 prior therapy. BRUKINSA was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.<sup>1,2</sup>

### STUDY 003

Study BGB-3111-AU-003 (Study 003) was a Phase 1/2 open-label, dose-escalation, global, multicenter, single-arm trial of 32 previously treated MCL patients enrolled in Australia, New Zealand, Europe, Asia, and the United States. BRUKINSA was given orally at starting doses of 160 mg twice daily or 320 mg daily. FDG-PET scans were not required for response assessment.<sup>1,3</sup>

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.<sup>1</sup>

ARs=adverse reactions; FDG-PET=fluorodeoxyglucose positron emission tomography.

## COMBINED DOSE REDUCTION AND DISCONTINUATION RATES

**Median duration of treatment: 17.5 months (range: 0.2-33.9 months)<sup>4</sup>**

Dose reductions due to ARs

**0.8%**

(1/118)  
of patients

Discontinuation rate due to ARs

**7%**

(8/118)  
of patients

Of the 118 MCL patients treated with BRUKINSA, 8 (7%) patients discontinued treatment due to ARs in the trials. The most frequent AR leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an AR leading to dose reduction (hepatitis B).<sup>1</sup>

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# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS

### 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.

### 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.

### 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.

### 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.

### 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.

### 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.

## ADVERSE REACTIONS

The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (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%).

## DRUG INTERACTIONS

**CYP3A Inhibitors:** When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

**CYP3A Inducers:** Avoid coadministration with moderate or strong CYP3A inducers.

## SPECIFIC POPULATIONS

**Hepatic Impairment:** The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

**References:** 1. BRUKINSA [package insert]. BeiGene, Ltd; 2019. 2. BeiGene. Study of evaluate efficacy and safety of BGB-3111 in subjects with relapsed or refractory mantle cell lymphoma (MCL). ClinicalTrials.gov website. NCT03206970. <https://clinicaltrials.gov/ct2/show/NCT03206970>. Last updated August 20, 2019. Accessed September 12, 2019. 3. BeiGene. Study of the safety and pharmacokinetics of BGB-3111 in subjects with B-cell lymphoid malignancies. ClinicalTrials.gov website. NCT02343120. <https://clinicaltrials.gov/ct2/show/NCT02343120>. Last updated May 31, 2019. Accessed September 12, 2019. 4. Data on file. BeiGene, Ltd. 2019.

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