Brukinsa®
zanubrutinib 80 mg capsules

FOR ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

THE COMPLETE DOSING AND ADMINISTRATION GUIDE

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.

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.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.

BRUKINSA Dosing Flexibility

2 Dosing Options[1]

Recommended dose is 320 mg daily.

Two 80-mg capsules TWICE DAILY		Four 80-mg capsules ONCE DAILY
am 160 mg + pm 160 mg	OR	320 mg

Can be coadministered with PPIs and H2-receptor antagonists

Administration[1]

- Can be taken with or without food. Can be taken with a high-fat meal—BRUKINSA drug concentration (AUC) is not affected
- Advise patients to swallow capsules whole with water—do not open, break, or chew capsules
- If a dose of BRUKINSA is missed, it should be taken as soon as possible with a return to the normal schedule the following day

BRUKINSA should be taken until disease progression or unacceptable toxicity occurs.

How Supplied and Storage[1]

Strength	Package Size	NDC Number
80 mg	120 capsules	72579-011-02

- 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)

Recommended Dose Adjustments

CYP3A Inhibitors or Inducers[1,2]

Coadministered Drug	Dose Adjustment
Moderate CYP3A inhibitors (such as erythromycin, fluconazole, and verapamil)	80 mg twice daily
Strong CYP3A inhibitors (such as clarithromycin and itraconazole)	80 mg once daily
Moderate CYP3A inducers (such as bosentan, efavirenz, and phenobarbital)	Avoid concomitant use
Strong CYP3A inducers (such as carbamazepine, phenytoin, and rifampin)	Avoid concomitant use

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

Hepatic Impairment[1]

Level of Impairment*	Dose Adjustment
Mild	None
Moderate	None
Severe	80 mg twice daily

*Based on Child-Pugh score.
AUC=area under the concentration-time curve; PPIs=proton pump inhibitors.

> No dose adjustment needed in patients with mild to moderate hepatic impairment

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

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.

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No Dose Adjustments With These Common Medications

Gastric Acid Reducing Agents[1]

Proton pump inhibitors
Including, but not limited to:

- Omeprazole
- Esomeprazole
- Lansoprazole

H2-receptor antagonists
Including, but not limited to:

- Famotidine
- Ranitidine
- Nizatidine

>60 million Americans experience acid indigestion at least once a month[3]

Anticlotting Medications[1,4]

Anticoagulants
Including, but not limited to:

- Heparins
- Direct thrombin inhibitors
- Factor Xa inhibitors
- Vitamin K antagonists

Antiplatelets
Including, but not limited to:

- Aspirin
- P2Y12 inhibitors
- Phosphodiesterase inhibitors
- PAR-1 antagonists

BRUKINSA was allowed to be coadministered in clinical trials with antiplatelets and anticoagulants (as long as INR was ≤1.5 and aPTT ≤1.5 x ULN).[4,5]

Coadministration of BRUKINSA with antiplatelet or anticoagulation medications may increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding.[1]

aPTT=activated partial thromboplastin time; CLcr=creatinine clearance; INR=International Normalized Ratio; PAR-1=protease-activated receptor 1; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

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.

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.

No Dose Adjustments Needed in Select Populations

Renal Impairment[1]

No dosage modification is recommended in patients with mild to moderate renal impairment.

Monitor for adverse reactions (ARs) in patients with severe renal impairment (CLcr<30 mL/min) or on dialysis.

Hepatic Impairment[1]

No dosage modification is recommended in patients with mild to moderate hepatic impairment.

The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment.

Recommended dose adjustment in patients with severe hepatic impairment is 80 mg twice daily.

Monitor for BRUKINSA ARs in patients with hepatic impairment.

Cardiac Impairment[1]

Monitor for signs and symptoms of atrial fibrillation or atrial flutter and manage as appropriate.

Hepatitis B and Hepatitis C[1,4]

Patients with serologic evidence of active hepatitis B (HBV) or hepatitis C (HCV) were excluded from study.

Infections due to hepatitis reactivation have occurred.

If hepatitis reactivation occurs, interrupt treatment with BRUKINSA.

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.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.

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Demonstrated Safety Profile in Clinical Trials

Combined ARs in ≥10% of Patients With MCL (N=118)[1]

Adverse Reactions	All Grades (%)	Grade ≥3 (%)
Upper respiratory tract infection	39	0
Neutropenia and Neutrophil count decreased	38	15
Rash	36	0
Thrombocytopenia and Platelet count decreased	27	5
Leukopenia and White blood count decreased	25	5
Diarrhea	23	0.8
Pneumonia	15	10
Anemia and Hemoglobin decreased	14	8
Musculoskeletal pain	14	3.4
Hypokalemia	14	1.7
Bruising	14	0
Constipation	13	0
Hypertension	12	3.4
Cough	12	0
Hemorrhage	11	3.4
Urinary tract infection	11	0.8

ARs of Special Interest in Patients With Hematologic Malignancies (N=629)[1,4]

Adverse Reactions	All Grades (%)	Grades ≥3 (%)
Atrial Fibrillation	2.0	0.6
Myalgia	3.7	0.6
Arthralgia	8.3	0.6
Headache	9.4	0.3

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

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.

Dose Modifications for ≥Grade 3 Adverse Reactions

ARs That Require Dose Modifications[1]

- 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)

Recommended Dose Modifications by Occurrence for ≥Grade 3 ARs[1]

Starting Dose		1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence
Start at 320 mg Total Dose (Four 80-mg capsules)		**No dose change**	**Reduce to 160 mg Total Dose**	**Reduce to 80 mg Total Dose**	**Discontinue**
		Resume treatment once toxicity has resolved to ≤Grade 1 or baseline			
Twice-daily Dosing	AM PM	AM PM	AM PM	once daily	**Discontinue**
	OR				
Once-daily Dosing				once daily	**Discontinue**

No dose exchange required for dose modification

Dose Reduction and Discontinuation Rates[1]

0.8% (1/118) of patients—dose reductions due to ARs

7% (8/118) of patients—discontinuation rate due to ARs

Median duration of treatment: 17.5 months (range: 0.2-33.9 months)[4]

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Flexible Dosing to Meet Patient Needs

Two flexible dosing options[1]

BRUKINSA can be taken as 160 mg twice daily or 320 mg once daily

No dose adjustments needed with common medications[1,4]

Gastric acid reducing agents | Anticlotting medications*

No dose exchange required for dose modifications[1]

Dose modification for ≥Grade 3 adverse reactions only requires reduction in number of capsules taken daily

myBeiGene® Patient Support

Dedicated Oncology Nurse Advocates provide personalized support for each patient's needs

The myBeiGene patient support program can provide your office with reimbursement and payment assistance to help your patients gain access to BRUKINSA.

To enroll in myBeiGene, please visit **BRUKINSA.com** or call **1-833-234-4363**.

IMPORTANT SAFETY INFORMATION

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%).

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aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; ULN=upper limit of normal.

References: 1. BRUKINSA [package insert]. BeiGene, Ltd; 2019. **2.** Drug development and drug interactions: table of substrates, inhibitors and inducers. US Food and Drug Administration. Updated March 10, 2020. Accessed July 8, 2020. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers **3.** Acid reflux. American College of Gastroenterology. Accessed May 12, 2020. https://gi.org/topics/acid-reflux/ **4.** Data on file. BeiGene, Ltd. 2019. **5.** BeiGene. Study of the safety and pharmacokinetics of BGB-3111 in subjects with B-cell lymphoid malignancies. ClinicalTrials.gov website. NCT02343120. Accessed September 12, 2019. https://clinicaltrials.gov/ct2/show/NCT02343120

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