Brukinsa®
zanubrutinib 80 mg capsules

THE COMPLETE DOSING AND ADMINISTRATION GUIDE

INDICATIONS

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

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) who have received at least one prior therapy
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen

The MCL and MZL indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has 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 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration 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: Unmatched BTKi dosing flexibility[1-4]

The Recommended Daily Dose of BRUKINSA Is 320 mg[1]

The only BTKi with dosing options[1]

Flexibility to tailor the schedule to your patients

ONCE DAILY

Consider for patients with compliance concerns or for those who prefer taking their medication once a day

320 mg daily dose

(four 80-mg capsules once daily)

TWICE DAILY

Consider for patients who take other twice-daily medications to maintain a consistent drug dosing schedule

320 mg daily dose

(two 80-mg capsules AM) + (two 80-mg capsules PM)

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.

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)

Straightforward Dose Adjustments

Hepatic Impairment[1]

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

The only BTKi with recommended dosage for severe hepatic impairment†[1-4]

CYP3A Inhibitors or Inducers[1,5]

Coadministered Drug	Dose Adjustment
Strong CYP3A inhibitors (such as clarithromycin and itraconazole)	80 mg once daily Interrupt dose as recommended for adverse reactions.
Moderate CYP3A inhibitors (such as erythromycin, fluconazole, and verapamil)	80 mg twice daily Modify dose as recommended for adverse reactions.
Strong CYP3A inducers (such as carbamazepine, phenytoin, and rifampin)	Avoid concomitant use
Moderate CYP3A inducers (such as bosentan, efavirenz, and phenobarbital)	Avoid concomitant use If these inducers cannot be avoided, increase BRUKINSA dose to 320 mg twice daily.
After discontinuation of a CYP3A inhibitor or inducer, resume previous dose of BRUKINSA.	

*Based on Child-Pugh score.

† Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.

AUC=area under the concentration-time curve; BTKi=Bruton's tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

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No Dose Adjustments Needed With These Common Medications

Anticlotting Medications[1,6]

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).[6-8]

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

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

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Infections (continued)

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii 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 (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, 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 (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

No Dose Adjustments Needed in Select Populations

Renal Impairment[1]

No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment (CrCl ≥15 mL/min).

Monitor for adverse reactions (ARs) in patients on dialysis.

Hepatic Impairment[1]

No dose adjustment is recommended in patients with mild to moderate hepatic impairment.

Recommended dose adjustment in patients with severe hepatic impairment is 80 mg twice daily. Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.

Monitor for ARs in patients with hepatic impairment.

Cardiac Arrhythmias[1]

Monitor for signs and symptoms of cardiac arrhythmias, manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

Hepatitis B (HBV) and Hepatitis C (HCV)[1,7]

Patients with serologic evidence of active HBV or HCV were excluded from BRUKINSA clinical studies.

Infections due to hepatitis reactivation have occurred. If reactivation occurs, interrupt treatment with BRUKINSA.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

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.

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

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Demonstrated Safety Profile in Clinical Trials

AEs in >10% of Patients With Hematologic Malignancies (N=1550)*[9]

Adverse Events	All Grades (%)	Grade ≥3 (%)
Upper respiratory tract infection	39	2
Hemorrhage	30	4
Neutropenia	28	19
Rash	28	0.9
Musculoskeletal pain	30	2
Bruising	23	0.1
Diarrhea	19	2
Cough	19	0.1
Thrombocytopenia	16	6
Pneumonia	20	11
Fatigue	17	1
Anemia	14	5
Urinary tract infection	13	2
Headache	11	0.4
Hypertension	14	7
Nausea	11	0.2
Dizziness	11	0.3
Abdominal pain	10	0.6

*Includes chronic lymphocytic leukemia, Waldenström's macroglobulinemia, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, and Richter's transformation.[7]

AE=adverse event.

AEs of Special Interest in Patients With Hematologic Malignancies (N=1550)[9]

Adverse Events	All Grades (%)	Grades ≥3 (%)
Arthralgia	14	0.7
Myalgia	4	0.4
Atrial fibrillation or atrial flutter	4	2

Dose Modifications for ≥Grade 3 Adverse Reactions

ARs That Require Dose Modifications[1]

- Grade 3 or Grade 4 febrile neutropenia
- Platelet count decreased to 25,000-50,000/mm^3 with significant bleeding
- Neutrophil count decreased to <500/mm^3†
- Platelet count decreased to <25,000/mm^3†
- Severe or life-threatening non-hematological toxicities‡

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 (160 mg twice daily or 320 mg once daily)	**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			

†Lasting more than 10 consecutive days.[1]
‡Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.[1]
§The recommended daily dose of BRUKINSA is 320 mg.[1]

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.[1]

No dose exchange required for dose modification[1]

Low rates of dose reductions or treatment discontinuation across BRUKINSA studies[1]

- Dose reductions: 0.8%-11%
- Treatment discontinuations: 2%-13%

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

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

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Flexible Dosing to Meet Patient Needs

Flexibility to tailor dosing schedule to your patients[1]

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

The only BTKi with recommended dosage for severe hepatic impairment*[1-4]

Adjust dose to 80 mg twice daily. No dose adjustment needed for mild to moderate hepatic impairment

Straightforward dose modifications without exchanges[1]

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

myBeiGene® Patient Support Program

Assisting you in providing complete support for patients taking BRUKINSA

To learn more, please visit **myBeiGene.com** or call **1-833-BEIGENE (1-833-234-4363)**.

IMPORTANT SAFETY INFORMATION (continued)

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 strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

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

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

*Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.[1]

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2023. **2.** CALQUENCE capsules. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **3.** CALQUENCE tablets. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **4.** IMBRUVICA. Package insert. Pharmacyclics LLC, Janssen Biotech, Inc; 2022. **5.** Drug development and drug interactions: table of substrates, inhibitors and inducers. US Food and Drug Administration. Updated August 24, 2022. Accessed September 28, 2022. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers **6.** Tam C, Opat S, Zhu J, et al. Pooled analysis of safety data from monotherapy studies of the Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib (BGB-3111), in B-cell malignancies. Poster presented at: European Hematology Association (EHA) 2019 Annual Meeting; June 13-16, 2019. Abstract PS1159. **7.** Data on file. BeiGene, Ltd; 2019. **8.** BeiGene. Study of the safety and pharmacokinetics of BGB-3111 in subjects with B-cell lymphoid malignancies. Clinicaltrials.gov website. NCT02343120. Last updated April 28, 2022. Accessed September 30, 2022. https://clinicaltrials.gov/ct2/show/NCT02343120 **9.** Data on file. BeiGene, Ltd; 2022.

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