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
- Relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy

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

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

BRUKINSA: UNMATCHED BTKi DOSING FLEXIBILITY

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

The Only BTKi With Dosing Options

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)

Dosing Schedule for BRUKINSA + obinutuzumab in FL[1,2]

BRUKINSA

320 mg daily dose
(until disease progression or unacceptable toxicity)

+

obinutuzumab

Cycle 1	Cycles 2-6	Maintenance
1000 mg Days 1, 8, and 15	**1000 mg** Day 1	**1000 mg** Every 8 weeks

Maximum total duration of obinutuzumab: ~30 months (maximum 20 doses)

In Cycle 1, obinutuzumab could be administered 100 mg on Day 1 and 900 mg on Day 2 at investigator discretion in ROSEWOOD (Study 212).
Refer to obinutuzumab prescribing information for additional dosing information.

Administration[1]

- Can be taken with or without food. BRUKINSA drug concentration (AUC) is not affected by high-fat meals
- 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)

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

MINIMAL DOSE ADJUSTMENTS IN SELECT SITUATIONS

Hepatic Impairment[1]

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

*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.

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

CYP3A Inhibitors or Inducers[1]

Coadministered Drug	Recommended BRUKINSA Dosage (Starting Dose: 160 mg twice daily or 320 mg once daily)
Clarithromycin 250 mg twice daily‡	80 mg twice daily§
Clarithromycin 500 mg twice daily	80 mg once daily§
Posaconazole suspension 100 mg once daily	80 mg twice daily§
Posaconazole suspension dosage higher than 100 mg once daily Posaconazole delayed-release tablets 300 mg once daily Posaconazole intravenous 300 mg once daily	80 mg once daily§
Other strong CYP3A inhibitor	80 mg once daily§
Moderate CYP3A inhibitor	80 mg twice daily§
Strong CYP3A inducer	Avoid concomitant use.
Moderate CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase BRUKINSA dose to 320 mg twice daily.
After discontinuation of a CYP3A inhibitor or moderate inducer, resume previous dose of BRUKINSA.	

‡Since clarithromycin 250 mg twice daily acts as a moderate CYP3A inhibitor, it is recommended that patients be administered clarithromycin 250 mg twice daily with 80 mg BRUKINSA twice daily.
§Modify or interrupt zanubrutinib dose as recommended for adverse reactions.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.8% of patients treated with BRUKINSA in clinical trials, with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% 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.

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[1,3,4]

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).

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

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; CLcr=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)

Hemorrhage (continued)

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 before and after surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia (7.9%), with fatal infections occurring in 3.2% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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 (21%), thrombocytopenia (8%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% 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.

NO DOSE ADJUSTMENTS NEEDED IN THESE SELECT SITUATIONS

Renal Impairment[1]

No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥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)[1,5]

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)

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA. The most frequent second primary malignancy was non-melanoma skin cancers (8%), followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 4.4% of patients treated with BRUKINSA, including Grade 3 or higher cases in 1.9% 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 0.3% 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.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

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=1729)*[5]

Adverse Events	All Grades (%)	Grade ≥3 (%)
Upper respiratory tract infection	38	3
Hemorrhage	32	4
Neutropenia	29	20
Rash	25	0.6
Musculoskeletal pain	24	2
Bruising	21	0.1
Diarrhea	20	2
Cough	20	0.1
Thrombocytopenia	19	7
Pneumonia	17	11
Fatigue	18	1
Anemia	15	6
Urinary tract infection	14	2
Headache	11	0.3
Hypertension	14	7
Nausea	11	0.2
Dizziness	11	0.3
Abdominal pain	11	0.9

*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.

AEs=adverse events.

AEs of Special Interest in Patients With Hematologic Malignancies (N=1729)[5]

Adverse Events	All Grades (%)	Grade ≥3 (%)
Arthralgia	14	0.6
Myalgia	4	0.3
Atrial fibrillation†	4	2

†Includes rates of atrial fibrillation only; does not include flutter.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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.

FLEXIBILITY TO MODIFY DOSE IN SMALL INCREMENTS

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§

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

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

<table>
<tr><th>Recommended Dose</th><th>1st Occurrence</th><th>2nd Occurrence</th><th>3rd Occurrence</th><th>4th Occurrence</th></tr>
<tr><td rowspan="2">320 mg Total Dose (160 mg twice daily or 320 mg once daily)</td><td>No dose change</td><td>Reduce to 160 mg Total Dose</td><td>Reduce to 80 mg Total Dose</td><td rowspan="2">Discontinue</td></tr>
<tr><td colspan="3">Resume treatment once toxicity has resolved to ≤Grade 1 or baseline</td></tr>
</table>

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

No dose exchange required for dose modification[1]

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.[1]

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

- Dose reductions: 0.8%-11%
- Treatment discontinuations: 2%-17%

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reactions (≥30%), including laboratory abnormalities, in patients who received BRUKINSA (N=1729) are decreased neutrophil count (51%), decreased platelet count (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

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

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UNMATCHED DOSE FLEXIBILITY TO MEET PATIENT NEEDS

The only BTKi with QD and BID dosing[1,6,7]
BRUKINSA provides flexibility to tailor the schedule to each patient

The only BTKi with recommended dosage for severe hepatic impairment*[1,6,7]
Adjust dose to 80 mg twice daily. No dose adjustment needed for mild to moderate hepatic impairment

Ability to dose reduce in small increments 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 coadministered 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 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.

References: 1. BRUKINSA. Package insert. BeiGene, USA, Inc.; 2024. **2.** Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: a phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. *J Clin Oncol*. 2023;41(33):5107-5117. **3.** Tam CS, 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. **4.** 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 January 31, 2024. https://clinicaltrials.gov/ct2/show/NCT02343120 **5.** Data on file. BeiGene, USA, Inc. **6.** CALQUENCE. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **7.** IMBRUVICA. Package insert. Pharmacyclics LLC, Janssen Biotech, Inc; 2024.

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