Brukinsa®
zanubrutinib 80 mg capsules

BRUKINSA PATIENT MANAGEMENT

This guide provides information that may help you manage potential adverse reactions (ARs) and side effects.

Information for BRUKINSA is based on data from the pooled safety population of 1550 patients across 9 clinical trials[1]

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.

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

COMMON ARs (≥30%) ASSOCIATED WITH ALL BTK INHIBITORS

The approved Bruton's tyrosine kinase inhibitors (BTKis) have distinct safety and tolerability profiles, but share 3 common adverse reactions: neutropenia, thrombocytopenia, and musculoskeletal pain.[1-4]

Common ARs are defined as those occurring in ≥30% of patients and appearing in the pooled safety populations in the package inserts of all 3 BTKis.

The rates of adverse events (AEs) across BRUKINSA studies were measured in a pooled safety population. Common AEs from BRUKINSA studies are listed in the table below.

COMMON AEs SHARED BY ALL BTKis[5]	Pooled Safety Population (N=1550)*	
	BRUKINSA All Grades (%)	BRUKINSA Grade ≥3 (%)
Neutropenia (Grouped Term)	28	19
Neutrophil Count Decreased	15	0.5
Neutropenia	15	19
Thrombocytopenia	16	6
Musculoskeletal Pain	30	2

*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.[5]

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.

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.

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.

MANAGEMENT OF COMMON ARs ASSOCIATED WITH BTK INHIBITORS

Below are general recommendations for managing common ARs associated with BTK inhibitors during treatment with BRUKINSA.

RECOMMENDATIONS FOR COMMON ARs[6]	
Neutropenia	Recommendations include antibiotics to prevent infections and white blood cell growth factors. Practicing good personal hygiene may lower the patient's risk of infection, including regularly washing hands and avoiding contact with people who are sick.
Thrombocytopenia	Recommendations include regular blood tests to monitor platelet counts, medications that may prevent low platelet counts, and transfusions for the temporary treatment of very low platelet counts. Additional prevention techniques include avoiding situations that could cause bleeding. Self-care methods such as using an extra soft toothbrush and brushing gently, shaving with an electric razor, avoiding activities that may cause injury, avoiding burns while cooking, and using a nail file instead of nail clippers may help to prevent bleeding when platelet counts are low.
Musculoskeletal Pain	Recommendations include using over-the-counter pain medicines, such as ibuprofen, naproxen, or acetaminophen or other medications such as muscle relaxers and corticosteroids. Some self-care and support methods to treat musculoskeletal pain include massage, physical therapy, exercise, acupuncture, and heat and cold.

BTK=Bruton's tyrosine kinase.

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AEs OF SPECIAL INTEREST

The rates of adverse events across BRUKINSA studies were measured in a pooled safety population. AEs of special interest from BRUKINSA studies are listed in the table below.

ADVERSE EVENTS[5]	Pooled Safety Population (N=1550)*	
	BRUKINSA All Grades (%)	BRUKINSA Grade ≥3 (%)
Diarrhea	19	2
Fatigue	17	1
Headache	11	0.4
Arthralgia	14	0.7
Myalgia	4	0.4
Afib/flutter	4	2

*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.[5]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

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.

MANAGEMENT OF ARs OF SPECIAL INTEREST

RECOMMENDATIONS FOR ARs OF SPECIAL INTEREST[6]	
Diarrhea	Recommendations include medications that may prevent and treat diarrhea, such as loperamide or a combination of diphenoxylate and atropine. Avoiding the following may help manage mild diarrhea: caffeine, alcohol, dairy, fat, fiber, orange juice, prune juice, and spicy foods.
Fatigue	Recommendations include lifestyle changes, dietary changes, working with a physical therapist or personal trainer, and medications or supplements that could help relieve fatigue. The following mind-body strategies may also help to reduce fatigue: yoga, acupuncture, massage, music therapy, and touch therapy.
Headache	Recommendations include pain relievers, tricyclic antidepressants, triptans, steroids, and antibiotics. The following may help reduce the number and severity of headaches: more sleep, changing diet, and reducing stress.
Arthralgia & Myalgia	Recommendations include pain relievers, corticosteroids, antibiotics, and certain anticonvulsants and antidepressants. Self-care and support methods, such as physical therapy, exercise, heat/cold, and massage may also help.

RECOMMENDATIONS FOR AFIB/FLUTTER[7]	
Afib/flutter	Recommendations include anticoagulation therapy after estimating the patient's risk of a thromboembolic event or major bleed. There is an increased risk of bleeding when combining BTKis with antiplatelet or anticoagulation therapy. Advise patients on antiplatelet or anticoagulation therapy to avoid taking medications such as NSAIDs, aspirin, vitamin E, fish oils, or flaxseed.

Afib=atrial fibrillation; NSAIDs=non-steroidal anti-inflammatory drugs.

Please also see dose modifications specific to BRUKINSA on the next page.

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

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STRAIGHTFORWARD DOSE MODIFICATIONS

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]

The recommended daily dose of BRUKINSA is 320 mg

No dose exchange required for dose modification; simply reduce the number of capsules[1]

IMPORTANT SAFETY INFORMATION

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%).

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.

LOW RATES OF DOSE REDUCTIONS AND TREATMENT DISCONTINUATIONS

Rates Across BRUKINSA Studies[1]

Dose reductions due to ARs ranged from

0.8%-11%

Discontinuation rates due to ARs ranged from

2%-13%

	Dose reduction rates due to ARs[1]	Discontinuation rates due to ARs[1]	Median duration of treatment[1,8-12]
CLL (TN)[†]	8%	8%	26 months
CLL (R/R)	11%	13%	30 months
WM (TN, R/R)[†]	11%	2%	25 months
MCL (R/R)	0.8%	7%	17.5 months
MZL (R/R)	2.3%	6%	14.5 months

[†]Cohort 1.[1]

Neutropenia Related Dose Reductions and Discontinuations[1,10,11]

No patients discontinued due to neutropenia in the TN CLL, MCL, and MZL studies. One patient in the WM study and 2 patients in the CLL R/R study discontinued due to neutropenia. Patients in studies received growth factor support as needed.

CLL=chronic lymphocytic leukemia; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; R/R=relapsed/refractory; TN=treatment naïve; WM=Waldenström's macroglobulinemia.

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

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2023. **2.** IMBRUVICA. Package insert. Pharmacyclics LLC, Janssen Biotech, Inc; 2022. **3.** CALQUENCE capsules. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **4.** CALQUENCE tablets. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **5.** Data on file. BeiGene, Ltd; 2022. **6.** American Society of Clinical Oncology. Managing physical side effects. Cancer.Net website. Accessed December 5, 2022. https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects **7.** American College of Cardiology. Anticoagulation for atrial fibrillation (AFib) in patients receiving Bruton tyrosine kinase (BTK) inhibitors. Created May 20, 2021. Accessed December 5, 2022. Reprinted with permission. © 2022 American Society of Clinical Oncology. All rights reserved. https://acc.bravais.com/s/CNJBxHNRDI2G7IxbkcSy **8.** Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2022;23(8):1031-1043. **9.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* Published online December 13, 2022. doi:10.1056/NEJMoa2211582 **10.** Data on file. BeiGene, Ltd; 2021. **11.** Data on file. BeiGene, Ltd; 2019. **12.** Data on file. BeiGene, Ltd; 2020.

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myBeiGene® Patient Support Program

Assisting you in providing complete support for patients after BRUKINSA has been prescribed

For patient enrollment and other program services, visit **myBeiGene.com** or call **1-833-BEIGENE (1-833-234-4363)**, M-F 8 AM - 8 PM ET, and speak with a dedicated Oncology Nurse Advocate.

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