Brukinsa® zanubrutinib 80mg capsules

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 largest pooled safety population in the BTKi class: 1729 patients across 9 clinical trials[1-4]

BTKi=Bruton's tyrosine kinase inhibitor.

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.

MOST 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 ARs: neutropenia, thrombocytopenia, and musculoskeletal pain.[2-4]

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 covalent BTKis.

COMMON ARs SHARED BY ALL COVALENT BTKis[1]	BRUKINSA All Grades (%)	BRUKINSA Grade ≥3 (%)
	Pooled Safety Population (N=1729)*	
Neutropenia (Grouped Term)	29	20
Neutrophil Count Decreased	15	9
Neutropenia	15	11
LOW RATES OF DISCONTINUATIONS DUE TO NEUTROPENIA—SEE DETAILS PAGE 7		
Thrombocytopenia	19	7
Musculoskeletal Pain	24	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.[1]

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.

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.

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[5]	
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.

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.

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

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AEs OF SPECIAL INTEREST

ADVERSE EVENTS[1]	BRUKINSA All Grades (%)	BRUKINSA Grade ≥3 (%)
	Pooled Safety Population (N=1729)*	
Rash	25	0.6
Diarrhea	20	2
Fatigue	18	1
Headache	11	0.3
Arthralgia	14	0.6
Myalgia	4	0.3
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.[1]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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.

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.

MANAGEMENT OF ARs OF SPECIAL INTEREST

RECOMMENDATIONS FOR ARs OF SPECIAL INTEREST[5]	
Rash	Recommendations include moisturizing skin creams, antihistamine medications, and/or steroids.
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[6]	
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.

AEs=adverse events; afib=atrial fibrillation; NSAIDs=non-steroidal anti-inflammatory drugs.

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

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

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FLEXIBILITY TO MODIFY DOSE IN SMALL INCREMENTS

ARs That Require Dose Modifications[2]

- 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.[2]

Recommended Dose Modifications by Occurrence for ≥Grade 3 ARs[2]

Recommended Dose	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence
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.[2]
†Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.[2]

No dose exchange required for dose modification; simply reduce the number of capsules[2]

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.[2]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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.

LOW RATES OF DOSE REDUCTIONS AND TREATMENT DISCONTINUATIONS

Rates Across BRUKINSA Studies[2]

Dose Reductions due to ARs Ranged From	Discontinuations due to ARs Ranged From
0.8%-11%	2%-17%

	Dose Reduction Rates due to ARs	Discontinuation Rates due to ARs	Median Duration of Treatment
CLL (TN)[†2,7]	8%	8%	26 months
CLL (R/R)[2,8]	11%	13%	30 months
WM (TN, R/R)[†1,2]	11%	2%	25 months
MCL (R/R)[1,2]	0.8%	7%	17.5 months
MZL (R/R)[1,2]	2.3%	6%	14.5 months
FL (R/R) in combination with obinutuzumab[2,9]	9%	17%	12.2 months

†Cohort 1.[2]

Neutropenia-Related Discontinuations[1,2]

No patients discontinued due to neutropenia in the TN CLL and R/R MCL and MZL studies. One patient in both the WM and FL studies 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; FL=follicular lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; R/R=relapsed/refractory; TN=treatment naïve; WM=Waldenström's macroglobulinemia.

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

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myBeiGene® Patient Support Program

Assisting you in providing complete support for patients taking BRUKINSA

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.

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.

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%).

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.

References: 1. Data on file. BeiGene USA, Inc. **2.** BRUKINSA. Package insert. BeiGene USA, Inc.; 2024. **3.** IMBRUVICA. Package insert. Pharmacyclics LLC, Janssen Biotech, Inc; 2024. **4.** CALQUENCE. Package insert. AstraZeneca Pharmaceuticals LP; 2022. **5.** American Society of Clinical Oncology. Managing physical side effects. Cancer.Net website. Accessed January 25, 2024. https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects **6.** American College of Cardiology. Anticoagulation for atrial fibrillation (AFib) in patients receiving Bruton tyrosine kinase (BTK) inhibitors. Created May 20, 2021. Accessed January 25, 2024. Reprinted with permission. © 2022 American Society of Clinical Oncology. All rights reserved. https://acc.bravais.com/s/CNJBxHNRDI2G7IxbkcSy **7.** 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. **8.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388(4):319-332. **9.** 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.

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