Brukinsa®
zanubrutinib 80 mg capsules

IN PREVIOUSLY TREATED MANTLE CELL LYMPHOMA (MCL)

BRUKINSA PATIENT MANAGEMENT

This guide provides information to help you manage adverse reactions (ARs) and minimize side effects.

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.

Please see Important Safety Information on the back page, and accompanying full Prescribing Information.

CLASS-RELATED ARs ASSOCIATED WITH BTK INHIBITORS

Bruton's tyrosine kinase (BTK) inhibitors share certain class side effects but still have distinct safety and tolerability profiles.[1-3] Hemorrhage, infections, cytopenias, and atrial fibrillation are common ARs of BTK inhibitors.[1-3] The rates for BRUKINSA are listed in the table below.

	Class-related ARs in patients with MCL (N=118)[1,4]		Class-related ARs in patients with hematological malignancies (N=629)*[1,4]	
ADVERSE REACTIONS	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Hemorrhage	11	3.4	10	1.3
Upper Respiratory Tract Infection†	39	0	38	2.5
Pneumonia†	15	10	18	9.4
Urinary Tract Infection†	11	0.8	13	2.1
Neutropenia and Neutrophil Count Decreased‡	38	15	34	22
Thrombocytopenia and Platelet Count Decreased‡	27	5	19	7
Leukopenia and White Blood Count Decreased‡	25	5	12	3.2
Anemia and Hemoglobin Decreased‡	14	8	16	7.6
Atrial Fibrillation and Flutter	1.7	0.8	2.0	0.6

	Class-related results in patients with MCL (N=118)[1,4]		Class-related results in patients with hematological malignancies (N=629)[1,4]	
LABORATORY ABNORMALITIES (change from baseline)	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Neutrophils Decreased	45	20	53	27
Platelets Decreased	40	6.8	39	10
Leukocytes Decreased	34	7.7	30	7.7
Hemoglobin Decreased	27	6.0	29	8.0

MANAGEMENT OF CLASS-RELATED ARs

Below are general recommendations for managing class-related ARs during treatment with BRUKINSA.

ADVERSE REACTIONS	MANAGEMENT OF ARs[1]
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	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.
Cytopenias	Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.
Atrial Fibrillation and Flutter	Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

*Chronic lymphocytic leukemia, Waldenström macroglobulinemia, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, and Richter's transformation.

†Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy.

‡Based on laboratory measurements. 40% (19/47) of patients with neutropenia used growth factor treatment. 30% (14/47) of patients with neutropenia had an infection.

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OTHER ARs OF SPECIAL INTEREST THAT MAY OCCUR DURING BTK THERAPY[1-3]

	ARs of special interest in patients with MCL (N=118)[1,4]		ARs of special interest in patients with hematological malignancies (N=629)[1,4]	
ADVERSE REACTIONS	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Diarrhea	23	0.8	20	1.0
Fatigue	7.6	0.8	11.3	0.8
Arthralgia	6.8	0	8.3	0.6
Myalgia	3.4	2.5	3.7	0.6
Headache	4.2	0	9.4	0.3

MANAGEMENT OF OTHER ARs OF SPECIAL INTEREST

ADVERSE REACTIONS	MANAGEMENT OF ARs: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) RECOMMENDATIONS[5]
Diarrhea	Recommendations include medications that may prevent and treat diarrhea, such as loperamide, as well as a combination of diphenoxylate and atropine. Avoiding the following may help manage mild diarrhea: caffeine, alcohol, dairy, fat, fiber, orange juice, prune juice, spicy foods, and medicines such as laxatives, stool softeners, and metoclopramide.
Fatigue	Recommendations include lifestyle changes, physical activity, dietary changes, working with a physical therapist or personal trainer, and certain 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.
Arthralgia	Recommendations include medications that may treat or reduce joint pain, such as 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.
Myalgia	Recommendations include medications that may treat muscle aches or reduce pain, such as pain relievers, muscle relaxants, corticosteroids, antibiotics, and antidepressants. Self-care and support methods such as physical therapy, exercise, heat/cold, and relaxation techniques may also help.
Headache	Recommendations include medications that may prevent and treat headaches or reduce pain, such as 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.

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BRUKINSA DOSE MODIFICATION FOR ≥GRADE 3 ARs

ARs That Require Dose Modification[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 Modification 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

BRUKINSA DOSE REDUCTION AND TREATMENT DISCONTINUATION RATES FOR MCL PATIENTS

Dose Reduction and Treatment Discontinuation Rates[1]

Dose reductions due to ARs

0.8%

(1/118) of patients

Discontinuation rate due to ARs

7%

(8/118) of patients

No patients discontinued due to neutropenia and 2 patients had febrile neutropenia. Patients on study received growth factor support as needed.[4]

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

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References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2019. **2.** CALQUENCE. Package insert. AstraZeneca Pharmaceuticals LP; 2019. **3.** IMBRUVICA. Package insert. Pharmacyclics LLC; 2020. **4.** Data on file. BeiGene, Ltd. 2019. **5.** American Society of Clinical Oncology. Managing physical side effects. Cancer.Net website. Accessed January 4, 2021. https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects

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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.

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.

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.

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.

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

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.

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%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

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 moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

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

INDICATION

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