

BRUKINSA® & BTK Inhibition



What is BRUKINSA®?

BRUKINSA® (zanubrutinib) is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) that is currently being evaluated in a broad late-stage clinical trials program globally as a monotherapy and in combination with other therapies to treat various B cell malignancies. BRUKINSA has been approved by the U.S. Food & Drug Administration (FDA) for the treatment of mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM) and marginal zone lymphoma (MZL).

BRUKINSA was discovered and developed by BeiGene, a global biotechnology company focused on developing innovative and affordable medicines to improve treatment outcomes and access for patients worldwide.

How Does BRUKINSA Work?

BTK is a key component of the B-cell receptor, or BCR, signaling pathway and is an important regulator of cell proliferation and cell survival in various B cell malignancies.¹

When cancer forms in B-cells, they often have too much BTK, which causes the cancerous cells to grow.²

BRUKINSA is a BTK inhibitor that blocks unusual BTK activity associated with malignant B-cell growth and survival. Because new BTK is continuously synthesized, BRUKINSA was specifically designed **to deliver complete and sustained inhibition of the BTK protein** by optimizing bioavailability, half-life, and selectivity.^{3,4}

Due to its specificity and improved target occupancy, BRUKINSA may offer improved tolerability compared to first-generation BTK inhibitors, and reduced frequency of certain cardiovascular adverse events.⁴

BRUKINSA Clinical Development Program

BRUKINSA has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease relevant tissues in studies.⁵ BeiGene's bold approach to clinical development—including two head-to-head trials^{6,7}—continues to generate evidence to support BRUKINSA's potential as a **best-in-class BTK inhibitor**.

Pivotal clinical trials of BRUKINSA include

- Fully-enrolled Phase 3 ASPEN clinical trial in patients with Waldenström's macroglobulinemia (WM) comparing zanubrutinib to ibrutinib (NCT03053440)
- Phase 3 ALPINE trial comparing zanubrutinib to ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (NCT03734016)

Pivotal clinical trials of BRUKINSA include (continued)

- Phase 3 SEQUOIA trial comparing zanubrutinib with bendamustine plus rituximab in patients with treatment-naïve (TN) CLL or SLL (NCT03336333)
- Phase 2 trial in combination with GAZYVA® (obinutuzumab) in patients with R/R follicular lymphoma (FL) (NCT03332017)
- Phase 3 trial comparing zanubrutinib and rituximab to bendamustine and rituximab in patients with untreated mantle cell lymphoma (MCL) (NCT04002297)
- Phase 2 MAGNOLIA trial in patients with R/R marginal zone lymphoma (MZL) (NCT03846427)
- Phase 2 trial (NCT04382586) in the U.S. comparing zanubrutinib plus supportive care, to placebo plus supportive care for the treatment of patients with COVID-19 disease and pulmonary distress
- Phase 2 ROSEWOOD trial (NCT03332017) in China comparing obinutuzumab and zanubrutinib vs obinutuzumab alone in treating patients with R/R FL
- Phase 2 trial (NCT03332173) in China in patients with WM
- Completed Phase 2 trials in China in patients with R/R MCL (NCT03206970) and R/R CLL or SLL (NCT03206918)

The broad BRUKINSA clinical program provides support for ongoing regulatory progress in the **United States, China, the European Union, and other countries or regions.**

BRUKINSA is approved in the following indications and regions

- ✓ For the treatment of MCL in adult patients who have received at least one prior therapy (United States, November 2019)*
- ✓ For the treatment of MCL in adult patients who have received at least one prior therapy (China, June 2020)**
- ✓ For the treatment of CLL or SLL in adult patients who have received at least one prior therapy (China, June 2020)**
- ✓ For the treatment of R/R MCL (United Arab Emirates, February 2021)
- ✓ For the treatment of WM in adult patients (Canada, March 2021)
- ✓ For the treatment of adult patients with WM who have received at least one prior therapy (China, June 2021)**
- ✓ For the treatment of MCL in adult patients who have received at least one prior therapy (Canada, July 2021)
- ✓ For the treatment of MCL in adult patients who have received at least one prior therapy (Chile, July 2021)
- ✓ For the treatment of WM in adult patients (United States, August 2021)
- ✓ For the treatment of MCL in adult patients (Brazil, September 2021)
- ✓ For the treatment of R/R MZL in adult patients who have received at least one anti-CD20-based regimen (United States, September 2021)*

* This indication was 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.

** This indication was approved under conditional approval. Complete approval for this indication may be contingent upon results from ongoing randomized, controlled confirmatory clinical trials.

Dosing and Administration

The recommended dose of BRUKINSA is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity. BRUKINSA capsules can be taken with or without food.

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 hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% 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 27% of patients, most commonly 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 (26%), thrombocytopenia (11%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% 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 monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 3.2% 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 1.1% 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 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, including laboratory abnormalities, in $\geq 30\%$ of patients who received BRUKINSA (N = 847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) 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 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.

INDICATIONS

- BRUKINSA 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.

- BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).
- BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

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 full U.S. Prescribing Information at www.beigene.com/PDF/BRUKINSAUSPI.pdf and Patient Information at www.beigene.com/PDF/BRUKINSAUSPPI.pdf.

References

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