

BRUKINSA[®] (zanubrutinib)

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What Is BRUKINSA?

BRUKINSA[®] (zanubrutinib) is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) discovered by BeiGene scientists that is currently being evaluated globally in a broad clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies.

BRUKINSA Approvals & Applications

BRUKINSA is approved in the United States (U.S.) for:



BRUKINSA is approved in 70 markets, including the U.S., China, European Union (EU), Great Britain, Canada, Australia, South Korea, and Switzerland, in selected indications and under development for additional indications globally. The MCL, MZL and FL indications are approved in the U.S. 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.

What Are B-cell Lymphomas?

- B cells (also known as B lymphocytes) are a type of white blood cell found in your blood and bone marrow.
- When B cells develop normally, they help protect the body from infection and disease.
- B-cell lymphomas, such as CLL/SLL, WM, MCL, MZL, and FL are caused by the growth and spread of abnormal, or cancerous, B cells.

What Is BTK?

- BTK is an important enzyme in the B-cell receptor signaling pathway, regulating cell proliferation and cell survival in various B-cell malignancies.ⁱ
- A BTK inhibitor (BTKi) is a targeted treatment that works to shut down (or inhibit) BTK, reducing the growth and survival of cancerous B cells.ⁱⁱ

How Does BRUKINSA Work?

- BRUKINSA was specifically designed to deliver targeted and sustained inhibition of the BTK protein by optimizing bioavailability, half-life, and selectivity.^{iii,iv}
- BRUKINSA is the only BTKi that can provide up to 100% inhibition. Inhibition was observed as 100% in human peripheral blood mononuclear cells with both once- and twice-daily dosing regimens, and inhibition in lymph nodes was 100% in twice-daily dosing regimens and 94% in once-daily regimens. It has the highest affinity for BTK and is more selective than first-generation BTKis with the lowest affinity for off-target kinases. The clinical significance of 100% inhibition has not been established.^{ii,iii}

How Was BRUKINSA Studied?

The global BRUKINSA development program includes more than 5,000 subjects enrolled to date in 29 countries and regions.

Key clinical trials include:

- **SEQUOIA** (Study BGB-3111-304) assessed the efficacy and safety of BRUKINSA compared to bendamustine plus rituximab in 589 adult patients with treatment-naïve CLL/SLL. SEQUOIA was a global Phase 3, randomized, open-label, multicenter trial.^{v,vi}
- **ALPINE** (Study BGB-3111-305) assessed the efficacy and safety of BRUKINSA versus ibrutinib in 652 adult patients with R/R CLL/SLL who had received ≥ 1 prior systemic therapy. ALPINE was a global Phase 3, randomized, open-label, multicenter trial.^{v,vi}
- **ASPEN** (Study BGB-3111-302) compared BRUKINSA with ibrutinib in 229 patients with WM. ASPEN was a Phase 3, randomized, open-label, multicenter trial conducted globally across 61 sites.^{v,viii}
- **MAGNOLIA** (Study BGB-3111-214) assessed the efficacy and safety of BRUKINSA in 68 patients with R/R MZL following at least one prior therapy. MAGNOLIA was a Phase 2, open-label, multicenter, single-arm trial.^{v,ix}
- **ROSEWOOD** (Study BGB-3111-212) is an ongoing global Phase 2 study of BRUKINSA plus obinutuzumab compared with obinutuzumab alone in 217 patients with R/R FL who received at least two prior lines of systemic therapy.^x
- **BGB-3111-AU-003** is a Phase 1/2, open-label, multiple-dose, dose escalation and expansion study to investigate the safety, tolerability, and pharmacokinetic profile and efficacy of BRUKINSA in patients with B-cell lymphoid malignancies.^{xi}
- **BGB-3111-GA101-001** is a Phase 1b study designed to assess the safety, tolerability, and antitumor activity of BRUKINSA with obinutuzumab in participants with B-cell lymphoid malignancies.^{xii}

U.S. Indications and Important Safety Information for BRUKINSA[®] (zanubrutinib)

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.

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.

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.

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% 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.

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 ($\geq 30\%$), 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 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.

Please see full [Prescribing Information](#) including [Patient Information](#).

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