BRUKINSA®
(zanubrutinib)

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Note: Any information on the products or the CLL disease contained herein is not intended to provide medical advice and/or treatment guidance.

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 is now FDA approved for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[1]

BRUKINSA is approved in more than 60 markets, including the United States, China, the European Union Great Britain, Canada, Australia, South Korea, Switzerland, and additional international markets. Additionally, regulatory submission are ongoing review around the world.[1]

What is BTK?

BTK, or Bruton's tyrosine kinase, is an important enzyme in the B-cell receptor signaling pathway, regulating cell proliferation and cell survival in various B cell malignancies, including CLL.[3]

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.[4,5]
- BRUKINSA is the only BTK inhibitor (BTKi) that can provide up to 100% inhibition. Inhibition 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 regimen and 94% in once-daily. It has the highest affinity for BTK, and is the most selective BTKi with the lowest affinity for off-target kinases.[4,5]

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.

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.

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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.

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 full Prescribing Information and Patient Information.

References:

1. BRUKINSA® (Zanubrutinib) Approved for the Treatment of Adults With CLL/SLL. https://ir.beigene.com/news/brukinsa-approved-in-the-u-s-for-chronic-lymphocytic-leukemia/4022a38f-ea68-4b11-ba1f-45478e2c0697/
2. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. doi:10.1056/NEJMoa2211582.
3. Moore, C. Donald, et al. "A Review of the Bruton Tyrosine Kinase Inhibitors in B-Cell Malignancies." Journal of the Advanced Practitioner in Oncology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8163255/. Accessed December 8, 2022.
4. Ou, C. Ying, et al. "Population Pharmacokinetic Analysis of the BTK Inhibitor Zanubrutinib in Healthy Volunteers and Patients With B Cell Malignancies." Clinical and Translational Science. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7993273/. Accessed July 7, 2021.
5. Guo, Yunhang, et al. "Discovery of Zanubrutinib (BGB-3111), a Novel, Potent, and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase." Journal of Medicinal Chemistry. https://pubmed.ncbi.nlm.nih.gov/31381333/ Accessed July 7, 2021.