BRUKINSA® (zanubrutinib)

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WHAT IS BRUKINSA?

BRUKINSA is an orally available, targeted treatment known as a Bruton's tyrosine kinase (BTK) inhibitor. With five FDA-approved indications and the broadest label in its class.

BRUKINSA is the **leader in the U.S. in new patient starts in both treatment-naïve and relapsed/refractory (R/R) chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL),** a global market expected to reach $12B+ by 2030.

It is also the **#1 prescribed BTK inhibitor across B-cell malignancies.**[i]

HOW BRUKINSA WORKS

BRUKINSA **works to shut down (or inhibit) the BTK protein.**

Shutting down the BTK protein is important because this protein sends non-stop signals to cancerous B cells to grow and spread.

BRUKINSA was **designed to block BTK signaling and keep it shut down around the clock.** This may help stop the signaling in cancerous B cells.

BRUKINSA has been **shown to block 100% of BTK in blood cells and 94% to 100% of BTK in lymph nodes** when taken at the recommended total daily dose of 320 mg. The clinical significance of blocking up to 100% of BTK on treatment responses has not been established.

With **differentiated pharmacokinetics** compared with other approved BTK inhibitors, BRUKINSA has been demonstrated to **inhibit the proliferation of malignant B cells** within a number of disease-relevant tissues.

FIVE FDA-APPROVED INDICATIONS IN ONLY FIVE YEARS

Chronic lymphocytic leukemia / small lymphocytic lymphoma	**Mantle cell lymphoma after at least one prior therapy***	**Waldenström's macroglobulinemia**	**R/R marginal zone lymphoma after at least one anti-CD20-based regimen***	**R/R FL, in combination with obinutuzumab, after two or more lines of systemic**

**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.*

Since its initial approval in 2019, **BRUKINSA has received five FDA-approved indications – the broadest label in its class** – and is now recognized as a best-in-class treatment option for patients with B-cell malignancies.

- BRUKINSA is the only BTK inhibitor approved for the treatment of follicular lymphoma (FL) and marginal zone lymphoma (MZL)

BRUKINSA is **approved in more than 70 markets,** including the EU, China, Great Britain, Canada, Australia, South Korea, and Switzerland, and over 140,000 patients have been treated with BRUKINSA to date.

DISCOVERING THE FULL POTENTIAL OF BRUKINSA

The global BRUKINSA clinical development program includes:

About **6,000 patients enrolled**

In **more than 35 trials**

In **30 countries and regions**

Confirmatory trials for BRUKINSA are underway to support continued approvals in the mantle cell lymphoma (MCL), MZL and FL indications (MANGROVE: NCT04002297; MAHOGANY: NCT05100862).

Regulatory submissions for the tablet formulation of BRUKINSA are currently under review in the United States and European Union (EU).

BRUKINSA is also being evaluated as part of the ongoing Phase 3 CELESTIAL-TNCLL study (NCT06073821) – the **only fixed-duration trial combining a BCL2 inhibitor (sonrotoclax) and BTK inhibitor (BRUKINSA) designed to show superiority against a contemporary and clinically relevant comparator** (venetoclax plus obinutuzumab).

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.

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.

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 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 U.S. Prescribing Information including U.S. Patient Information.

[i] As of November 12, 2024, based on reported sales from Q3 2024 earnings. BeiGene Announces Third Quarter 2024 Financial Results and Corporate Updates – NASDAQ (US) Website.