35-MONTH EFFICACY AND SAFETY UPDATE[1]

THE BTK INHIBITOR DEMONSTRATED TO PROVIDE COMPLETE AND SUSTAINED INHIBITION[2,3]

FOR ADULTS WITH PREVIOUSLY TREATED MANTLE CELL LYMPHOMA (MCL)*

24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.[2,3]

*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.

Powerful Responses With Consistent Results†

Initial analysis (18 months)‡

STUDY **206** | PET-BASED[2]

84% ORR (95% CI: 74, 91) **59%** CR

Assessed by IRC

STUDY **003** | CT-BASED[2]

84% ORR (95% CI: 67, 95) **22%** CR

Assessed by IRC

Long-term analysis (35 months)§

STUDY **206** | PET-BASED[1]

84% ORR (95% CI: 74, 91) **78%** CR

Assessed by investigator

Demonstrated Safety Profile

The overall safety profile was unchanged at 35 months[1,2]

Dose reductions due to adverse reactions[2] **0.8%** (1/118) of patients

Discontinuation rate due to adverse reactions[2] **7%** (8/118) of patients

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

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias.

The most common adverse reactions (≥30%) included decreased neutrophil count, upper respiratory tract infection, decreased platelet count, hemorrhage, decreased lymphocyte count, rash, and musculoskeletal pain.

Flexible Dosing to Meet Patient Needs

2 flexible dosing options[2]

BRUKINSA® (zanubrutinib) can be taken as 160 mg twice daily or 320 mg once daily

No dose adjustments needed with several common medications[2,4-6]

- Gastric acid reducing agents including PPIs, H2RAs, and antacids
- Anticlotting medications¶

No dose exchange required for dose modification[2]

Dose modification for ≥Grade 3 adverse reactions only requires reduction in number of capsules taken daily

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

†The efficacy of BRUKINSA was assessed in 2 clinical trials that included a total of 118 adult patients with MCL who received at least 1 prior therapy. Study **206**: N=86, Phase 2, open-label, multicenter, single-arm trial; PET scans were required for response assessment. Study **003**: N=32, Phase 1/2, open-label, global, multicenter, single-arm trial; PET scans were not required for response assessment and the majority of patients were assessed mostly using CT scans.

‡Median follow-up time for initial analysis was 18.4 months for Study 206 and 18.8 months for Study 003.[4]

§Median follow-up time for long-term analysis was 35.3 months for Study 206.[1]

¶BRUKINSA was allowed to be coadministered in clinical trials with antiplatelets and anticoagulants (as long as INR was ≤1.5 and aPTT ≤1.5 x ULN).

aPTT=activated partial thromboplastin time; BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; CT=computed tomography; H2RAs=H2-receptor antagonists; INR=International Normalized Ratio; IRC=independent review committee; ORR=overall response rate; PBMCs=peripheral blood mononuclear cells; PET=positron emission tomography; PPIs=proton pump inhibitors; ULN=upper limit of normal.

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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 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 ≥ 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 co-administration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid co-administration 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

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 full Prescribing Information including Patient Information.

References: 1. Song Y, Zhou K, Zou D, et al. Zanubrutinib in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Poster presented at: European Hematology Association (EHA) 2021 Virtual Congress; June 9-17, 2021. Abstract EP789. **2.** BRUKINSA. Package insert. BeiGene, Ltd; 2021. **3.** Tam C, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. **4.** Data on file. BeiGene, Ltd. 2019. **5.** BeiGene. Study of the safety and pharmacokinetics of BGB-3111 in subjects with B-cell lymphoid malignancies. ClinicalTrials.gov website. NCT02343120. Last updated May 19, 2021. Accessed May 24, 2021. https://clinicaltrials.gov/ct2/show/NCT02343120 **6.** Smelick GS, Heffron TP, Chu L, et al. Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development. *Mol Pharm*. 2013;10(11):4055-4062.

Brukinsa® zanubrutinib 80mg capsules

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