On behalf of BeiGene, Ltd., I respectfully request the NCCN (CLL/SLL Guidelines Panel) to review the enclosed materials for the inclusion of BRUKINSA™ (zanubrutinib) for the treatment of patients with CLL/SLL.

I would also like to acknowledge the contributions of the NCCN panel members who are investigators on zanubrutinib clinical studies and co-authors or co-contributors to some of these publications.

Specific Change: Please consider the inclusion of zanubrutinib as a treatment option for first-line CLL/SLL with del(17p)/TP53 mutation and for relapsed/refractory CLL/SLL with/without del(17p)/TP53 mutation (Category 2A).

FDA Clearance: On November 14, 2019, zanubrutinib was approved by the FDA under the brand name BRUKINSA™ for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.1 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. Zanubrutinib is not currently approved by the FDA for the treatment of CLL/SLL.

Rationale: Zanubrutinib is a potent, selective, and irreversible oral BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases.2,3

Data from the nonrandomized cohort of the phase 3 study in patients with previously untreated CLL/SLL:4
- In the global, phase 3, open-label SEQUOIA study (BGB-3111-304, NCT03336333), a nonrandomized cohort of 109 treatment-naïve patients with CLL/SLL harboring del(17p) were treated with zanubrutinib 160 mg twice daily (Arm C).
- Patients had a median age of 70 years (range, 42-86); 38.5% had bulky disease.
- As of August 7, 2019, after a median follow-up of 10 months, ORR was 92.7% (CR 1.9%, PR 78.9%, PR-L 11.9%). The median time to response was 2.8 months; duration of response was ≥6 months in 95% of patients. Median PFS was not reached.

Data from the global phase 1/2 study in treatment-naïve or relapsed/refractory CLL/SLL patients:2,5
- BGB-3111-AU-003 (NCT02343120) was a global, multicenter, phase 1/2 study of zanubrutinib in patients with B-cell malignancies. The results for 94 patients with CLL/SLL were previously published.2
- A recent update was presented at ASH 2019; study enrollment was complete with a total of 123 CLL/SLL patients. Patients had a median age of 67 years (range, 24-87); 17.1% were ≥75 years old; 38.2% had bulky disease.
- As of May 8, 2019, the median follow-up was 29.5 months; the median treatment duration was 25.8 months.
- In the overall CLL/SLL population, ORR was 95.9% (CR 15.4%, CRi 0.8%, PR 73.2%, PR-L 6.5%) with response improving over time; 97.2% of responders remained in response at 12 months. Among the 16 patients with del(17p); ORR was 93.8% (CR 6.3%, PR 75%, PR-L 12.5%); 100% of responders remained in response at 12 months.
- In the 22 treatment-naïve CLL/SLL patients, ORR was 100% (CR 22.7%, PR 77.3%); 95.2% of responders remained in response at 12 months. At a median PFS follow-up of 32.2 months, the estimated PFS rates at 12 and 24 months were 95%. Among the 3 treatment-naïve patients with del(17p), ORR was 100% (all PR), and all remained in response at 12 months.
- Among the 101 patients with relapsed/refractory CLL/SLL, the median number of prior therapies was 2 (range, 1-10). Del(17p), TP53 mutation, del(11q), and unmutated IGHV were present in 16.2%, 31%, 23.5% and 68.3% of patients, respectively. ORR was 95% (CR 13.9%, CRi 1%, PR 72.3%, PR-L 7.9%); 97.6% of responders remained in response at 12 months. At a median PFS follow-up of 23.1 months, the estimated PFS rates at 12 and 24 months were 97% and 91%, respectively. In the 13 relapsed/refractory CLL/SLL patients with del(17p), ORR was 92.3% (CR 7.7%, PR 69.2%, PR-L 15.4%); all responders remained in response at 12 months.5
Data from the phase 2 study conducted in China with patients with relapsed/refractory CLL/SLL:

- The single-arm, open-label, multicenter, phase 2 BGB-3111-205 study (NCT03206918) included 91 patients in China with relapsed/refractory CLL/SLL. Patients received zanubrutinib 160 mg twice daily.
- Patients had a median age of 61 years (range, 35-87); 79.1% had disease refractory to last therapy, and 44.4% had bulky disease. TP53 mutation/del(17p) was present in 24.4% of patients.
- As of December 14, 2018, after a median follow-up of 15.1 months, ORR was 84.6% (CR 3.3%, PR 59.3%, PR-L 22%). Median PFS was not reached; the PFS rates at 6 and 12 months were 92.2% and 87.2%, respectively.
- ORR was 86.4% in patients with del(17p) and 82.4% in patients with unmutated IGHV.

Summary of cumulative safety experience with zanubrutinib:

- In a pooled safety analysis conducted in 682 patients with B-cell malignancies treated in 6 ongoing zanubrutinib monotherapy studies (including MCL, WM, CLL/SLL, DLBCL, and others), patients had a median age of 64 years with 15% aged ≥75 years (range, 20-90), and most patients (91%) had relapsed/refractory disease.
- The median duration of zanubrutinib exposure was 13.4 months; 57% of patients had ≥12 months of exposure; 5% were treated for ≥36 months. The median relative dose intensity was 99.8% (range, 99.1-100).
- The most common adverse events reported in ≥10% of patients were upper respiratory tract infection, absolute neutrophil count (ANC) decreased, diarrhea, cough, contusion, rash, anemia, platelet count decreased, urinary tract infection, white blood cell count decreased, constipation and fatigue.
- Opportunistic infections reported in >1 patient were herpes simplex, bronchopulmonary aspergillosis, and cryptococcal meningitis.
- Adverse events of special interest including atrial fibrillation/flutter, major hemorrhage, and grade ≥3 hypertension were reported in 1.9%, 2.5%, and 3.4% of patients treated with zanubrutinib monotherapy, respectively. The exposure-adjusted incidence rates were 0.13 events/100 patient-months for atrial fibrillation/flutter of any grade, 0.17 events/100 patient-months for major hemorrhage of any grade, and 0.24 events/100 patient-months for grade ≥3 hypertension. Patients have been allowed to receive anticoagulant and antiplatelet agents.

Please refer to the BRUKINSATM package insert for the FDA-approved indication, dosage and administration, and safety information. Additional references are submitted in support of the proposed change, including the high-level information on the comparative safety data for zanubrutinib vs. ibrutinib in the global phase 3 study in WM.

References