zanubrutinib (Brukinsa™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO172

Description

Zanubrutinib (Brukinsa) is an orally administered Bruton's Tyrosine Kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months (first three months split fill)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zanubrutinib (Brukinsa)	Mantle cell lymphoma in adults who have received at least one prior therapy	80 mg capsule	120 capsules/30 days
	Waldenström's macroglobulinemia in adults		
	Chronic lymphocytic leukemia or small lymphocytic lymphoma in adults		
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen		

Initial Evaluation

I. **Zanubrutinib (Brukinsa)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, or hematologist; **AND**
   C. Medication will not be used in combination with any other oncolytic medication; **AND**
   D. Member has not previously progressed on a BTK inhibitor [e.g., ibrutinib (Imbruvica), acalabrutinib (Calquence)]; **AND**
   E. A diagnosis of one of the following:
      1. **Waldenström's Macroglobulinemia (WM)**; **AND**
         i. Member has received one prior therapy [e.g., chemotherapy, rituximab (Rituxan)]; **OR**

ii. Provider attestation that member is not a candidate for standard immunochemotherapy based on documented risk factors or comorbidities

2. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL); AND**
   i. Medication is used in previously untreated CLL/SLL; **AND**
      a. The member does not have a del17p mutation; **OR**
   ii. Medication is used in the relapsed/refractory CLL/SLL; **AND**
      a. Member has received one prior therapy [e.g., chemotherapy, venetoclax (Venclexta), obinutuzumab (Gazyva)]

II. Zanubrutinib (Brukinsa) is considered investigational when used for all other conditions, including but not limited to:
   A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation
   B. Diffuse Large B-cell Lymphoma (DLBCL)
   C. Follicular Lymphoma (FL)
   D. Hairy Cell Leukemia (HCL)
   E. Graft-versus Host Disease (GvHD)
   F. Marginal Zone Lymphoma (MZL)
   G. Indolent Non-Hodgkin Lymphoma (iNHL)
   H. MCL monotherapy
   I. MCL first-line therapy
   J. MCL combination therapy
   K. Richter's Transformation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., no signs of disease progression); **AND**
IV. Zanubrutinib (Brukinsa) will not be used in combination with any other oncolytic medication

Supporting Evidence

I. **WM:**

A. Zanubrutinib (Brukinsa) is FDA-approved for WM based on the non-comparative assessment of DOR from zanubrutinib (Brukinsa) treatment arms and was granted Fast Track and Orphan Drug designation.
B. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 77 WM patients and one head-to-head trial against ibrutinib (ASPEN). ASPEN was a Phase 3, randomized, active control, open-label trial which enrolled 137 relapsed/refractory (RR) and 37 treatment naïve WM adult patients. Median number of previously tried therapies included 1 (range: 1-8) and majority (90%) were refractory to anti-CD20 therapies (rituximab, ofatumumab), alkylating agents (88%) (cyclophosphamide, chlorambucil, bendamustine), and glucocorticoids (72%). Treatment naïve patients consisted of those unsuitable for standard immunochemotherapy based on presence of comorbidities or risk factors precluding its use (e.g., age, cardiac, renal, infection comorbidities). Median patient age was 70 years of age. The trial excluded patients with previous exposure to BTK inhibitor therapy and those with WM central nervous system involvement. The primary endpoint of proportion of patients achieving very good partial response (VGPR) or CR was not reached. The trial efficacy analysis used hierarchical sequence; thus, all secondary endpoints were considered exploratory. Secondary endpoint of median PFS was not estimable, but 18-month PFS was 85% for zanubrutinib (Brukinsa) and 84% for ibrutinib. Median OS was not estimable at the time of analysis, but 18-month OS was 97% for zanubrutinib (Brukinsa) and 93% for ibrutinib.
C. Zanubrutinib (Brukinsa) had lower rates of atrial fibrillation (2% vs 15%), hypertension (11% vs 16%), minor bleeding (48.5% vs 59.2%), major hemorrhage (5.9% vs 9.2%), and diarrhea (20.8% vs 31.6%) compared to ibrutinib, respectively. The rate of neutropenia was 29.7% and 13.3% for zanubrutinib (Brukinsa) and ibrutinib, respectively.
D. NCCN guidelines recommend the following preferred therapies for the treatment of primary, and previously treated, WM: bendamustine/rituximab, bortezomib/dexamethasone/rituximab, ibrutinib ± rituximab (category 1), rituximab/cyclophosphamide/dexamethasone, and zanubrutinib (Brukinsa) (category 1).

II. **CLL/SLL:**

A. Efficacy and safety of zanubrutinib (Brukinsa) in treatment naïve CLL/SLL without a del17p mutation is established based on one Phase 3, open-label, randomized, active-controlled (cohort 1) trial (SEQUOIA). Enrolled patients (N=590) had untreated CLL/SLL, were ≥65 years of age or ≥18 years of age with comorbidities and were considered unsuitable for fludarabine-cyclophosphamide-rituximab treatment (defined as 65 years or older, a Cumulative Illness Rating Scale [CIRS] score of more than 6, creatinine clearance less than 70 mL/min, or history of severe or frequent infections). Patients in cohort 1 were without del17p mutation and were randomized 1:1 to zanubrutinib (Brukinsa) 160mg BID or bendamustine and rituximab (BR). Patients in cohort 2 (single-arm, open label portion of trial) had del17p mutation and underwent treatment with zanubrutinib (Brukinsa) by itself.

As of December 2022, results are available for a median follow-up of 26.2 months. Median PFS and OS were not reached in any treatment group. Estimated PFS at 24 months was statistically superior for zanubrutinib (Brukinsa) as compared to BR (85.5% vs 69.5%) p<0.001. In cohort 1, the difference in PFS between the treatment groups was not significant among patients with mutated IGHV, small subgroup of patients with SLL, and those with pathogenic TP53 mutation. Estimated OS at 24 months did not reach statistical significance between groups, (94.3% vs 94.6%) p=0.87. The estimated PFS at 24 months for cohort 2 was 88.9%. Efficacy in patients with del17p mutation (cohort 2) remain undefined as results are considered observational due to lack of comparator arm. Grade 3 serious adverse events occurred more frequently in patients treated with BR those treated with zanubrutinib (Brukinsa) (31% vs 20%). Incidence of Grade 3 neutropenia was higher with BR than zanubrutinib (Brukinsa) (22% vs 5%). Grade 1-2 bleeding and cardiac adverse events occurred more frequently with zanubrutinib (Brukinsa) than with BR (41% vs 9%) and (10% vs 6%), respectively. Several patients who reported major bleeding adverse events were treated with anticoagulants which may confound this safety data. Rates of cardiac arrhythmias with zanubrutinib (Brukinsa) in this study were consistent with those observed in other large, randomized studies of second-generation BTK inhibitors, including zanubrutinib (Brukinsa) and acalabrutinib (Calquence), in B-cell malignancies.

B. Zanubrutinib (Brukinsa) was studied in one phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 101 patients with treatment relapsed/refractory CLL or SLL; one phase 2, open-label, single-arm trial (BGB-3111-205) in 91 Chinese patients with relapsed/refractory CLL or SLL; and one phase 3, randomized, open-label, head-to-head study against ibrutinib (ALPINE). The ALPINE study included 652 adult patients with relapsed/refractory CLL or SLL who have tried ≥1 prior systemic therapy consisting of ≥2 cycles of treatment. The median age was 67 years (range, 35 to 90), 73% had unmutated immunoglobulin heavy-chain variable region (IGHV) status, and 23% had a chromosome 17p deletion, TP53 mutation, or both. The median number of previous lines of therapy was 1 (range, 1 to 12). The percentage of patients with an overall response (ORR), as assessed by the independent review committee were higher in the zanubrutinib (Brukinsa) group than in the ibrutinib group (86.2% vs 75.7%). At 24 months, the percentage of patients with progression-free survival, as assessed by the investigators, was 78.4% (95% CI, 73.3 to 82.7) in the zanubrutinib (Brukinsa) group and 65.9% (95% CI, 60.1 to 71.1) in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib (Brukinsa) group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group. Results were consistent in the high-risk population of patients with 17p deletion, TP53 mutation, or both. The percentages of patients who were alive without disease progression at 24 months in the high-risk population were 72.6% (95% CI, 60.3 to 81.7) in the zanubrutinib (Brukinsa) group and 54.6 (95% CI, 40.7 to 66.4) in the ibrutinib group. As of the data-cutoff date in the final analysis, fewer deaths had been reported in

the zanubrutinib (Brukinsa) group than in the ibrutinib group (48 and 60). Overall survival was not different in the two groups (hazard ratio for death 0.76; 95% CI, 0.51 to 1.11); longer follow-up is warranted to determine any differences between the treatments with respect to overall survival. The median overall survival had not been reached in either treatment group. Safety profile was comparable between the two treatment arms except, zanubrutinib (Brukinsa) had a higher incidence of Grade ≥3 adverse events compared to ibrutinib: neutropenia (16% vs 13.9%) and hypertension (14.8% vs 11.1%). There was a lower incidence of Grade ≥3 atrial fibrillation/flutter (1.9% vs 3.7%), serious events leading to treatment discontinuation (15.4% vs 22.2%) and events leading to death (10.2% vs 11.1%) in zanubrutinib (Brukinsa) vs ibrutinib treatment groups.

Investigational or Not Medically Necessary Uses

I. The following indications do not have sufficient evidence to support the use of zanubrutinib (Brukinsa) at this time:
   A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation
      1. The safety and efficacy in patients with del17p mutation was studied in cohort 2 (Group C) of the SEQUOIA trial. Estimated PFS at 24 months was 88.9% (95% CI: 81.3-93.6). Estimated OS at 24 months was 93.6% (95% CI: 87.1-96.9). Due to the open label, single-arm trial design with respect to the cohort 2 population, safety and efficacy remains observational and is undetermined at this time.
   B. Diffuse Large B-cell Lymphoma (DLBCL)
   C. Follicular Lymphoma (FL)
   D. Hairy Cell Leukemia (HCL)
   E. Graft-versus Host Disease (GvHD)
   F. Marginal Zone Lymphoma (MZL)
      1. For the treatment of MZL, zanubrutinib (Brukinsa) is FDA-approved under the accelerated approval pathway based on ORR and DOR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Finalized data have not been published on these trials at this time.
      2. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies including 20 previously treated MZL patients (BGB-3111-AU-003) and one Phase 2, open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least 1 prior anti-CD20-based regimen (MAGNOLIA). MAGNOLIA study included patients with a median age of 70 years (range: 37 to 85), 38% had extranodal MZL, 38% nodal,

18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 88% of patients having prior rituximab-based chemotherapy, 32% had refractory disease at study entry. ORR was reached in 45 (68.2%) patients while DOR was not reached at the time of data analysis. Twelve-month DOR, PFS, and OS was as 93.0%, 82.5%, and 95.3%, respectively.

3. The most common adverse events were similar to adverse events seen in clinical trials studying other cancer types and included diarrhea, contusion, constipation, pyrexia, and upper respiratory tract infections. Serious adverse events occurred in 38.2% of patients and included COVID-19 pneumonia, pyrexia, and fall. Four patients discontinued treatment due to adverse events and 29.4% of patients had dose interruption due to adverse events.
4. Treatment of MZL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trials (single-arm, open-label study designs) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MZL.
5. NCCN guidelines recommend anti-CD20 based regimens as preferred therapies in second-line and subsequent setting as well as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ibrutinib, lenalidomide + rituximab, and zanubrutinib with a Category 2A recommendation. Other recommend regimens additionally umbralisib and PI3K inhibitors in patients relapsed/refractory after 2 prior therapies.

G. Indolent Non-Hodgkin Lymphoma (iNHL)

H. MCL monotherapy

1. For the treatment of MCL, zanubrutinib (Brukinsa) was FDA-approved under the accelerated approval pathway based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials; however, finalized data has not been published on these trials at this time.
2. Zanubrutinib (Brukinsa) was studied in one open-label, single-arm, Phase 2 trial (BGB-3111-206), and one Phase 1/2 safety and pharmacokinetic trial (BGB-3111-AU-003) in 118 patients with MCL who had progressed on prior systemic therapy. The primary efficacy outcome was ORR which was 84% in both trials. Secondary efficacy outcomes were complete response (CR), partial response (PR), and duration of response (DOR). The percentage of patients with a CR was 59% and 22% for the Phase 2 trial and Phase 1/2 trial, respectively. The percentage of patients with a PR was 24% and 62% for the Phase 2 trial and Phase 1/2 trial, respectively. Median DOR in months was 19.5 and 18.5 for the Phase 2 trial and

Phase 1/2 trial, respectively. Progression-free survival was evaluated in the Phase 2 trial and found 74.6% of patients at 12 months were progression-free.

3. Treatment of MCL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trial (single-arm, open-label study design) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MCL.

I. MCL first-line therapy
J. MCL combination therapy
K. Richter's Transformation

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed criterion requiring use of other BTKi before Brukinsa in relapsed/refractory CLL/SLL. Added previously untreated CLL/SLL indication and associated criteria. Added previously untreated CLL/SLL with del17p mutation as E/I. Changed the length of initial approval from three to six months. Updated supporting evidence section.	12/2022
Removed initial criteria and moved MCL indication to experimental or not medically necessary uses section.	01/2022
Added initial criteria for non-FDA approved indication of CLL/SLL and updated supporting evidence. Added Richter's Transformation in the E/I section.	12/2021
Added expanded indication of Waldenström's macroglobulinemia (WM) in the initial evaluation criteria. Updated supporting evidence section to include clinical trial information for WM. Added supporting evidence for the expanded indication of marginal zone lymphoma (MZL) in investigational uses section.	11/2021
Policy created	02/2020