PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Oral – Bruton's Tyrosine Kinase Inhibitor) – Brukinsa Prior Authorization Policy
- Brukinsa® (zanubrutinib capsules and tablets – BeOne Medicines)

REVIEW DATE: 06/11/2025; selected revision 06/18/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Brukinsa, a Bruton's tyrosine kinase inhibitor (BTK), is indicated for the treatment of the following: [1]

- **Chronic lymphocytic leukemia or small lymphocytic lymphoma,** in adults.
- **Follicular lymphoma,** relapsed or refractory, in combination with Gazyva® (obinutuzumab intravenous infusion), after two or more lines of systemic therapy in adults.
- **Mantle cell lymphoma,** in adults who have received at least one prior therapy.
- **Marginal zone lymphoma**, relapsed or refractory, in adults who have received at least one anti-CD20-based regimen.
- **Waldenström Macroglobulinemia,** in adults.

The follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma indications are approved as accelerated approvals based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines

Brukinsa is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[4]

- **B-Cell Lymphomas**: NCCN guidelines (version 2.2025 – February 10, 2025) address classic follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma.[2]
    - **Follicular lymphoma**: The guidelines recommend Brukinsa + Gazyva as third-line and subsequent therapy for no response, relapsed, or progressive disease in patients with indications for treatment as "other recommended regimens" for classic follicular lymphoma (category 2A).
    - **Mantle cell lymphoma**: Brukinsa + Venclexta® (venetoclax tablets) + Gazyva is recommended as induction therapy with a classical or indolent *TP53* mutation in absence of a clinical trial (category 2A). Brukinsa is also recommended as "preferred" aggressive induction therapy in combination with chemotherapy (TRIANGLE regimen: alternating RCHOP [rituximab, cyclosporine, doxorubicin, vincristine, and prednisone] + (category 2B). Brukinsa + rituximab is recommended as maintenance therapy (category 2B). Brukinsa is a "preferred" regimen for second-line or subsequent therapy (category 2A). There is a footnote that states that Brukinsa or Calquence® (acalabrutinib tablets) has not been shown to be effective for Imbruvica® (ibrutinib tablets, capsules, or oral solution) refractory mantle cell lymphoma with *BTK* C481S mutations. Rituximab + covalent BTK inhibitors (Calquence, Imbruvica, or Brukinsa) can be used as pre-treatment in order to limit the number of cycles of aggressive induction therapy with R-HyperCVAD regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) [category 2A].
    - **Marginal zone lymphoma**: The guidelines recommend Brukinsa as a "preferred" regimen as second-line and subsequent therapy for patients who have relapsed, refractory, or progressive disease after at least one prior anti-CD20 monoclonal antibody (mAB)-based regimen (category 2A), including older or infirm patients when tolerability of combination chemoimmunotherapy is a concern.
- **Central Nervous System (CNS) Cancers**: NCCN guidelines (version 1.2025 – June 3, 2025) recommend Brukinsa ± high-dose cytarabine for relapsed or refractory primary CNS lymphoma as "useful in certain circumstances" as treatment with autologous stem cell reinfusion (category 2A).
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** NCCN guidelines (version 3.2025 – April 2, 2025) recommend single-agent Brukinsa as first-line "preferred" regimen for patients without 17p deletion/TP53 mutation (category 1) and with 17p deletion/TP53 mutation (category 2A). Brukinsa is also recommended as second-line and subsequent therapy

"preferred" regimen for patients with or without 17p deletion/TP53 mutation (category 1).[3] In the second-line and subsequent therapy setting, there is a footnote, which states that Brukinsa or Calquence have not been shown to be effective for Imbruvica-refractory chronic lymphocytic leukemia with BTK C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Brukinsa or Calquence without recurrence of symptoms. Brukinsa is also recommended in combination with Tevimbra® (tislelizumab-jsgr intravenous infusion) for histologic (Richter) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) in patients with del(17p)/TP53 mutation, or who are chemotherapy refractory or unable to receive chemoimmunotherapy (category 2A).

- **Hairy Cell Leukemia**: NCCN guidelines (version 1.2025 – September 26, 2024) recommend single-agent Brukinsa for patients with progressive disease after relapsed/refractory therapy as "other recommended regimens" (category 2A).[5]
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma**: NCCN guidelines (version 3.2025 – February 6, 2025) recommend single-agent Brukinsa as a "preferred" regimen for primary therapy and previously treated disease (category 1).[6] Brukinsa is also recommended for symptomatic management of Bing Neel Syndrome as a "preferred" regimen (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Brukinsa. All approvals are provided for the duration noted below.

- **Brukinsa® (zanubrutinib capsules and tablets - BeOne Medicines)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Chronic Lymphocytic Leukemia.** Approve for 1 year if the patient is ≥ 18 years of age.

2. **Follicular Lymphoma**. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least two other systemic regimens AND
   Note: Examples of systemic regimens contain one or more of the following products: bendamustine, Gazyva (obinutuzumab intravenous infusion), rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, lenalidomide, chlorambucil, or Tazverik (tazemetostat tablets).

C) This medication will be used in combination with Gazyva (obinutuzumab intravenous infusion).

3. **Mantle Cell Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i, ii, iii, or iv):
      i. Patient has tried at least one systemic regimen; OR
      Note: Examples of a systemic regimen contain one or more of the following products: rituximab, dexamethasone, cytarabine, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, bendamustine, bortezomib, or lenalidomide.
      ii. According to the prescriber, patient is not a candidate for a chemotherapy regimen; OR
      iii. Brukinsa is being used in combination with rituximab; OR
      iv. Patient meets BOTH of the following (a and b):
         a) Patient has a *TP53* mutation; AND
         b) The medication is used as induction therapy in combination with Venclexta (venetoclax tablets) and Gazyva (obinutuzumab intravenous infusion).

4. **Marginal Zone Lymphoma**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   Note: Marginal zone lymphoma includes gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one systemic regimen.
   Note: Examples of a systemic regimen contain one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, lenalidomide, Gazyva (obinutuzumab intravenous infusion) or Imbruvica (ibrutinib tablets, capsules, or oral solution).

5. **Small Lymphocytic Lymphoma.** Approve for 1 year if the patient is ≥ 18 years of age.

6. **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

7. **Hairy Cell Leukemia**. Approve for 1 year if the patient meets ALL of the following (A, B and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has received at least one systemic therapy for relapsed or refractory disease; AND
   Note: Examples of therapy include: clinical trial, Tafinlar (dabrafenib capsules or oral tablets for suspension) + Mekinist (trametinib tablets and oral solution),

Zelboraf (vemurafenib tablets), rituximab, Pegasys (peginterferon alfa-2a subcutaneous injection), cladribine, Nipent (pentostatin intravenous infusion).

C) Patient has progressive disease.

8. **Primary Central Nervous System Lymphoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient ≥ 18 years of age; AND
   B) Patient has tried at least one systemic regimen; AND
   C) The medication is used in combination with autologous stem cell reinfusion.

CONDITIONS NOT COVERED

- **Brukinsa® (zanubrutinib capsules and tablets - BeOne Medicines)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available

REFERENCES

1. Brukinsa® capsules and tablets [prescribing information]. San Mateo, CA: BeOne Medicines; June 2025.
2. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 2.2025 – February 10, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 9, 2025.
3. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2025 – April 2, 2025). © 2025 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on June 9, 2025.
4. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 9, 2025. Search term: zanubrutinib.
5. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2025 – September 26, 2024). © 2024 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on June 9, 2025.
6. The NCCN Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2025 – February 6, 2025). © 2025 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on June 9, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Follicular Lymphoma:** Condition of approval and criteria were added to FDA-approved indication section due to new FDA indication for relapsed or refractory follicular lymphoma, in combination with Gazyva® (obinutuzumab intravenous infusion), after two or more lines of systemic therapy in adults. **Mantle Cell Lymphoma:** Criteria which states that this medication is being used in combination with rituximab and being used as pre-treatment in order to limit the number of cycles of induction therapy with RHyperCVAD regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was added an option for approval. **Hairy Cell Leukemia:** Condition of approval and criteria were added to Other Uses with Supportive Evidence.	03/13/2024
Selected Revision	**Mantle Cell Lymphoma**: The following criteria were added as an option for approval, "Patient has a *TP53* mutation and the medication is used as induction therapy in combination with Venclexta (venetoclax tablets) and Gazyva (obinutuzumab intravenous infusion)."	06/12/2024
Early annual revision	**Mantle Cell Lymphoma**: For a patient who is using Brukinsa in combination with rituximab, the following criterion requirement that this medication is being used as pre-treatment in order to limit the number of cycles of induction therapy with RHyperCVAD regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was removed.	01/29/2025
Update	**04/08/2025**: The policy name was changed from "Oncology – Brukinsa PA Policy" to "Oncology (Oral - Bruton's Tyrosine Kinase Inhibitor) – Brukinsa PA Policy".	--
Early Annual Revision	**Follicular Lymphoma:** Doxorubicin was added to the Note of examples of systemic regimen. **Mantle Cell Lymphoma:** The wording of "systemic regimen" was reworded to "chemotherapy regimen" for the option of approval which previously stated "according to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail)." **Primary Central Nervous System Lymphoma:** Condition of approval and criteria were added to Other Uses with Supportive Evidence.	06/11/2025
Selected Revision	The tablet formulation was added to the policy and criteria. **Mantle Cell Lymphoma:** The wording "i.e., an elderly patient who is frail" was removed from the requirement which previously stated, "according to the prescriber, patient is not a candidate for a chemotherapy regimen (i.e., an elderly patient who is frail)."	06/18/2025