PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Brukinsa Prior Authorization Policy
- Brukinsa® (zanubrutinib capsules – BeiGene)

REVIEW DATE: 03/13/2024; selected revision 06/12/2024

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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 conditions: [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's Macroglobulinemia,** in adults.

Guidelines

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

- **B-Cell Lymphomas**: NCCN guidelines (version 1.2024 – January 18, 2024) address classic follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma.[2] The guidelines recommend Brukinsa + Gazyva as third line and subsequent therapy as "Other Recommended Regimens" for classic follicular lymphoma (category 2A). The guidelines recommend Brukinsa as a "Preferred Regimen" among several as second line and subsequent therapy for marginal zone lymphoma for patients who have relapsed/refractory disease after at least one prior anti-CD20 monoclonal

antibody (mAB)-based regimen (category 2A). For mantle cell lymphoma, 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-refractory mantle cell lymphoma with *BTK* C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Brukinsa or Calquence without recurrence of symptoms. Rituximab + covalent BTK inhibitors (Calquence, Imbruvica [ibrutinib tablets, capsules, or oral solution], or Brukinsa) can be used as pre-treatment in order to limit the number of cycles of induction therapy with R-HyperCVAD regimen (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) [category 2A]. Brukinsa in combination with Venclexta (venetoclax tablets) and Gazyva® (obinutuzumab intravenous infusion) is also recommended as induction therapy for mantle cell lymphoma with a classical or indolent *TP53* mutation (category 2A) in absence of a clinical trial.[5]

- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** NCCN guidelines (version 2.2024 – March 11, 2024) 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.
- **Hairy Cell Leukemia**: NCCN guidelines (version 1.2024 – November 3, 2023) 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 2.2024 – December 5, 2023) recommend single-agent Brukinsa as a primary "Preferred Regimen" (category 1).[6] The guidelines also recommend Brukinsa as a "Preferred Regimen" option for previously treated disease (category 1). 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 (BeiGene)**

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, 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, cisplastin, oxaliplatin, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, bendamustine, bortezomib, lenalidomide
      ii. According to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly patient who is frail); OR
      iii. Patient meets BOTH of the following (a and b):
         a) This medication is being used in combination with rituximab; AND
         b) 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).
      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 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), Zelboraf (vemurafenib tablets),

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

C) Patient has progressive disease.

CONDITIONS NOT COVERED

- **Brukinsa® (zanubrutinib capsules (BeiGene)**

is(are) considered experimental, investigational, or unproven for ANY other use(s).

REFERENCES

1. Brukinsa® capsules [prescribing information]. San Mateo, CA: BeiGene; March 2024.
2. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 1.2024 – January 18, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 12, 2024.
3. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 2.2024 – March 11, 2024). © 2024 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on March 12, 2024.
4. The NCCN Drugs and Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 12, 2024. Search term: zanubrutinib.
5. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2024 – November 3, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on March 12, 2024.
6. The NCCN Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 2.2024 – December 5, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on March 12, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Mantle Cell Lymphoma:** An alternative option of approval was added to the requirement for a trial of one systemic regimen that according to the prescriber, the patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail).	04/19/2023
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