PHARMACY COVERAGE GUIDELINE

BRUKINSA™ (zanubrutinib) oral capsule
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Brukinsa (zanubrutinib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist
2. Individual is 18 years of age or older
3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Mantle Cell Lymphoma (MCL) in those who have received at least one prior therapy
    b. Waldenström's macroglobulinemia (WM)

c. Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen

d. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

e. Relapsed or refractory follicular lymphoma (FL), in combination with Gazyva (obinutuzumab), after two or more lines of systemic therapy

f. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Negative pregnancy test in a woman of childbearing potential
   b. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Brukinsa (zanubrutinib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Serious hemorrhagic events including intracranial, gastrointestinal, hematuria, or hemothorax
   b. Serious infection including bacterial, viral, or fungal and opportunistic infections

c. Severe neutropenia, thrombocytopenia, leukopenia, or anemia
d. Serious cardiac arrhythmias

6. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Brukinsa (zanubrutinib) is 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. Brukinsa (zanubrutinib) is also indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM). Brukinsa (zanubrutinib) is also indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen. 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. Brukinsa (zanubrutinib) is also indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Brukinsa (zanubrutinib) is also indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy.

Brukinsa (zanubrutinib) is a highly selective Bruton tyrosine kinase (BTK) inhibitor. Brukinsa (zanubrutinib) forms a covalent bond with a cysteine residue in the BTK active site to inhibit BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK signals activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Brukinsa (zanubrutinib) inhibits malignant B-cell proliferation and reduces tumor growth.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

NCCN recommendation definitions:
Category 1:

Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Eastern Co-operative Oncology Group (ECGO) Performance Status:

Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead
Oken, MM, Creech, RH, Tormey, DC, et al.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

Bruton's kinase inhibitors:

Drug Name	FDA-Approved Uses
Calquence (acalabrutinib)	MCL, CLL/SLL
Imbruvica (ibrutinib)	MCL, CLL/SLL, WM, MZL, cGVHD
Jaypirca (pirtobrutinib)	MCL
Brukinsa (zanubrutinib)	MCL, WM, MZL
MCL = Mantle cell lymphoma CLL = Chronic lymphocytic leukemia SLL = Small lymphocytic lymphoma WM = Waldenström's macroglobulinemia MZL = Marginal zone lymphoma cGVHD = Chronic graft versus host disease	

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Generic Equivalent (if available)

Resources:

Brukinsa (zanubrutinib) product information, revised by BeiGene USA, Inc. 06-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 04, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas Version 1.2025 – Updated December 20, 2024. Available at https://www.nccn.org. Accessed February 03, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2025 – Updated December 18, 2024. Available at https://www.nccn.org. Accessed February 03, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2025 –Updated October 01, 2024. Available at https://www.nccn.org. Accessed February 03, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.