Clinical Policy: Zanubrutinib (Brukinsa)

Reference Number: CP.PHAR.467
Effective Date: 03.01.20
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Zanubrutinib (Brukinsa®) is a Bruton tyrosine kinase (BTK) inhibitor.

FDA Approved Indication(s)

Brukinsa is indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy*
- Waldenström's macroglobulinemia (WM)
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen*
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- Relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy*

**This indication is approved under accelerated approval based on overall response rate and for FL, also durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Brukinsa is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Mantle Cell Lymphoma (*B-cell lymphoma subtype*) (must meet all)**:**

1. Diagnosis of MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b, or c):
   a. As a single agent therapy, and member has received ≥ 1 prior therapy (*see Appendix B)*;
   b. In combination with rituximab;
   c. As a component of TRIANGLE regimen (*see Appendix D*);
5. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;

6. If disease is positive for BTK C481S mutation: Member has not had previous disease progression on Imbruvica®;
7. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (must meet all)**:**

1. Diagnosis of WM or lymphoplasmacytic lymphoma (LPL, off-label);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Brukinsa is not prescribed concurrently with Imbruvica or Calquence®;
6. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. Marginal Zone Lymphoma (*B-cell lymphoma subtype*) (must meet all)**:**

1. Diagnosis of one of the following MZL subtypes (a, b, c, or d):
   a. Gastric MALT lymphoma;
   b. Nongastric MALT lymphoma (noncutaneous);
   c. Nodal MZL;
   d. Splenic MZL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as single agent therapy;
5. Disease is releapsed, refractory, or progressive;
6. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Member has received ≥ 1 line of systemic therapy including an anti-CD20 agent (e.g., rituximab/rituximab biosimilar)* *(see Appendix B)*;

   **Prior authorization may be required*

8. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

D. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (must meet all)**:**
1. Diagnosis of CLL/SLL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as single agent therapy;
5. If disease is positive for BTK C481S mutation: Member has not had previous disease progression on Imbruvica;
6. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

E. Follicular Lymphoma (*B-cell lymphoma subtype*) (must meet all):
1. Diagnosis of FL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Gazyva®;
5. Disease is relapsed, refractory or progressive;
6. Member has received ≥ 2 prior lines of systemic therapy (*see Appendix B)*;
7. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;

8. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

F. Hairy Cell Leukemia (off-label) (must meet all)**:**
1. Diagnosis hairy cell leukemia;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as single agent therapy;
5. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

G. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Brukinsa for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For brand Brukinsa requests, member must use generic zanubrutinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. New dose does not exceed 320 mg (4 capsules) per day;
   b. If co-administered with a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, phenobarbital, primidone), dose does not exceed 640 mg (8 capsules) per day;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BTK: Bruton tyrosine kinase
CLL: chronic lymphocytic leukemia

FDA: Food and Drug Administration
FL: follicular lymphoma
LPL: lymphoplasmacytic lymphoma
MCL: mantle cell lymphoma
MZL: marginal zone lymphoma
NCCN: National Comprehensive Cancer Network
SLL: small lymphocytic lymphoma
WM: Waldenström's macroglobulinemia

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
MCL		
RDHA/RCHOP (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)/(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate/ cytarabine) + rituximab	Varies	Varies
NORDIC (rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone/rituximab + cytarabine)	Varies	Varies
RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)	Varies	Varies
Bendeka® (bendamustine) + Rituxan® (rituximab)	Varies	Varies
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)	Varies	Varies
RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
Revlimid® (lenalidomide) + Rituxan® (rituximab)	Varies	Varies
MZL		
Bendeka® (bendamustine) + Rituxan® (rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
CVP (cyclophosphamide, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
Rituxan® (rituximab)	Varies	Varies
FL		
Bendeka® (bendamustine) + Gazyva® (obinutuzumab) or Rituxan® (rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Gazyva® (obinutuzumab) or Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
CVP (cyclophosphamide, vincristine, prednisone) + Gazyva® (obinutuzumab) or Rituxan® (rituximab)	Varies	Varies
Revlimid® (lenalidomide) + Rituxan® (rituximab)	Varies	Varies
Rituxan® (rituximab)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- TRIANGLE regimen: Alternating RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + covalent BTKi/RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MCL, WM, MZL, CLL, SLL, FL	160 mg PO BID or 320 mg PO QD	320 mg/day 640 mg/day when used with a moderate CYP3A4 inducer

VI. Product Availability
Capsule: 80 mg

VII. References
1. Brukinsa Prescribing Information. San Mateo, CA; BeiGene USA, Inc.; March 2024. Available at www.brukinsa.com. Accessed March 15, 2024.
2. Zanubrutinib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed March 14, 2024.
3. National Comprehensive Cancer Network Guidelines. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed March 15, 2024.
4. National Comprehensive Cancer Network Guidelines. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed March 15, 2024.
5. National Comprehensive Cancer Network Guidelines. B-cell lymphomas Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed March 15, 2024.
6. National Comprehensive Cancer Network Guidelines. Hairy Cell Leukemia Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed November 22, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.07.20	02.20
1Q 2021 annual review: oral oncology generic redirection language added; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.09.20	02.21
Added off-label indication for CLL/SLL per NCCN guidelines.	05.07.21	
1Q 2022 annual review: RT4: criteria added for new FDA approved indications: WM and MZL; modified "Medical justification…" to "Member must use…"; references reviewed and updated.	10.14.21	02.22
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
Per NCCN Compendium added off label use in LPL; for WM, LPL, MZL added requirement that Brukinsa is not prescribed concurrently with Calquence. Template changes applied to other diagnoses/indications.	08.23.22	11.22
1Q 2023 annual review: Per NCCN Compendium added monotherapy criterion to MCL, MZL, and CLL/SLL indications, and removed intolerance/contraindication to other BTK inhibitors criterion from CLL/SLL criteria as Brukinsa is a preferred regimen for CLL/SLL; for MCL and CLL/SLL, add requirement for no previous disease progression on Imbruvica and positive for BTK C481S mutation per NCCN; removed requirement that Brukinsa is not prescribed concurrently with Calquence or Imbruvica from MZL indication as the monotherapy requirement was added; for MZL added requirement for previous anti-CD20 therapy to align with PI and NCCN; from references reviewed and updated.	10.20.22	02.23
RT4: updated policy to reflect now FDA-approved indication of CLL/SLL, which was previously included in policy as off-label; added maximum dose option if co-administered with a moderate CYP3A4 inducer; clarified that if disease is positive for BTK C481S mutation, member has not had previous disease progression on Imbruvica for indications of MCL and CLL/SLL.	02.13.23	
1Q 2024 annual review: added criteria for hairy cell leukemia per NCCN; updated MCL regimens in Appendix B; references reviewed and updated.	10.13.23	02.24
RT4: added new FDA-approved indication for FL; for MCL, added option to be prescribed in combination with ritixumab or as a component of TRIANGLE regimen per NCCN; for MZL, added criterion that disease is releapsed, refractory, or progressive per NCCN and PI; references reviewed and updated.	03.15.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.