# Clinical Policy: Venetoclax (Venclexta)

Reference Number: CP.PHAR.129
Effective Date: 07.17.18
Last Review Date: 11.22
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

## Description

Venetoclax (Venclexta®) is a B-cell lymphoma 2 protein (BCL-2) inhibitor.

## FDA Approved Indication(s)

Venclexta is indicated:

- For the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

## 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 Venclexta is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** (must meet all)**:**

1. Diagnosis of CLL or SLL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a or b):*
   a. Prescribed as first-line therapy in combination with Gazyva®;
   b. Prescribed as subsequent therapy for relapsed/refractory disease in combination with rituximab or as a single agent (*see Appendix B for examples of prior therapy*);
   **Prior authorization may be required.*
6. Request meets one of the following (a or b):*
   a. Dose does not exceed both of the following (i and ii):
      i. 400 mg per day;
      ii. 4 tablets per day;
   b. 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. Myeloid Leukemias** (must meet all)**:**
1. Diagnosis of one of the following myeloid leukemias (a or b):
   a. AML;
   b. Blastic plasmacytoid dendritic cell neoplasm (BPDCN);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. If diagnosis is AML, one of the following (a, b, or c):
   a. Disease is newly diagnosed, and (i or ii):
      i. Age ≥ 60 years;
      ii. Medical justification supports inability (*see Appendix D for examples*) to use intensive induction chemotherapy (*see Appendix B for examples*);
   b. Disease has relapsed after or is in remission following Venclexta therapy;
   c. Disease has relapsed after or is refractory to induction therapy (*see Appendix B for examples*);*
      **Prior authorization may be required.*
6. If diagnosis is BPDCN, one of the following (a or b):
   a. Disease is systemic, and request is for palliative treatment (e.g., member has low performance and/or nutritional status [i.e., serum albumin < 3.2 g/dL; not a candidate for intensive remission therapy or tagraxofusp-erzs]);
   b. Disease is relapsed/refractory;
7. Prescribed in combination with azacitidine, decitabine, or low-dose (20 mg/m$^2$) cytarabine;*
   **Prior authorization may be required.*
8. Request meets one of the following (a, b, or c):*
   a. In combination with azacitidine or decitabine: Dose does not exceed both of the following (i and ii):
      i. 400 mg per day;
      ii. 4 tablets per day;
   b. In combination with low-dose cytarabine: Dose does not exceed both of the following (i and ii):
      i. 600 mg per day;
      ii. 6 tablets 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. Mantle Cell Lymphoma (off-label)** (must meet all)**:**
1. Diagnosis of mantle cell lymphoma;

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Member has received ≥ 1 prior therapy (*see Appendix B for examples*);*
   **Prior authorization may be required.*
6. Prescribed as a single agent or in combination with rituximab or ibrutinib;
7. 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

**D. Multiple Myeloma (off-label)** (must meet all)**:**
1. Diagnosis of multiple myeloma with t(11;14) translocation;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Member has received ≥ 1 prior therapy (*see Appendix B for examples*);*
   **Prior authorization may be required.*
6. Prescribed in combination with dexamethasone;
7. 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

**E. Additional NCCN Recommended Uses (off-label)** (must meet all)**:**
1. Diagnosis of one of the following (a or b):
   a. Systemic light chain amyloidosis that is relapsed/refractory;
   b. Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma as a single agent;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Member has received ≥ 1 prior therapy (*see Appendix B for examples*);*
   **Prior authorization may be required.*
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

**F. 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 Venclexta for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For brand Venclexta requests, member must use generic venetoclax, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. For AML, prescribed in combination with azacitidine, decitabine, or low-dose (20 mg/m$^2$) cytarabine;*
   **Prior authorization may be required.*
5. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. CLL, SLL, or in combination with azacitidine or decitabine for AML: New dose does not exceed both of the following (i and ii):
      i. 400 mg per day;
      ii. 4 tablets per day;
   b. In combination with low-dose cytarabine for AML: New dose does not exceed both of the following (i and ii):
      i. 600 mg per day;
      ii. 6 tablets 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*).

**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*

AML: acute myeloid leukemia
BCL-2: B-cell lymphoma 2 protein
BPDCN: blastic plasmacytoid dendritic cell neoplasm
CLL: chronic lymphocytic leukemia
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
SLL: small lymphocytic lymphoma

*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 |
|---|---|---|
| **CLL/SLL**<br>*Examples of first-line, second-line and subsequent therapies:*<br>• FCR (fludarabine, cyclophosphamide, rituximab) | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| • HDMP (high-dose methylprenisolone) + rituximab<br>Single-agent examples: Imbruvica® (ibrutinib); Campath® (alemtuzumab) ± rituximab; Gazyva; Copiktra® (duvelisib); Calquence® (acalabrutinib); Revlimid® (lenalidomide) ± rituximab; Arzerra® (ofatumumab) ± FC (fludarabine, cyclophosphamide); Leukeran® (chlorambucil) + rituximab; Zydelig® (idelalisib) ± rituximab | | |
| **AML**<br>cytarabine with idarubicin or daunorubicin<br><br>cytarabine with idarubicin or daunorubicin or mitoxantrone | Age < 60 years: example of intensive induction therapy: cytarabine 100 – 200 mg/m$^2$ continuous IV infusion x 7 days with idarubicin 12 mg/m$^2$ IV or daunorubicin 60-90 mg/m$^2$ IV x 3 days<br><br>Age ≥ 60 years: example of intensive induction therapy: cytarabine 100 – 200 mg/m$^2$ continuous IV infusion x 7 days with idarubicin 12 mg/m$^2$ IV or daunorubicin 60-90 mg/m$^2$ IV x 3 days or mitoxantrone 12 mg/m$^2$ x 3 days | Varies |
| **Mantle cell lymphoma**<br>Examples of induction/chemoimmuno-therapy:<br>• RDHA (rituximab, dexamethasone, cytarabine) + platinum therapy (e.g., carboplatin, cisplatin, oxaliplatin)<br>• Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin) | Varies | Varies |
| **Multiple myeloma**<br>Examples of primary therapy: | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| • Bortezomib/cyclophosphamide or lenalidomide/dexamethasone<br>• Carfilzomib or ixazomib/lenalidomide/ dexamethasone<br>• Daratumumab/lenalidomide/ dexamethasone ± bortezomib<br>• Lenalidomide/dexamethasone<br>• Daratumumab/bortezomib/ mephalan/prednisone<br>• Daratumumab/cyclophosphamide /bortezomib/dexamethasone<br>Examples of maintenance therapy:<br>• Lenalidomide<br>• Ixazomib<br>• Bortezomib | | |
| **Systemic light chain amyloidosis**<br>Examples of primary therapy:<br>• Darzalex Faspro® (daratumumab and hyaluronidase-fihj)/ bortezomib/cyclophosphamide/ dexamethasone, bortezomib/ cyclophosphamide/dexamethasone, melphalan/dexamethasone | Varies | Varies |
| **Waldenström macroglobulinemia / lymphoplasmacytic lymphoma**<br>Examples of primary therapy:<br>• Brukinsa® (zanubrutinib), Imbruvica® (ibrutinib) ± rituximab, bendamustine/rituximab, bortezomib/dexamethasone/ 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*

- Contraindication(s): concomitant use of Venclexta with strong inhibitors of CYP3A at initiation and during ramp-up phase in patients with CLL/SLL
- Boxed warning(s): none reported

*Appendix D: General Information*

Patient or disease state characteristics that may preclude use of intensive induction therapy include but are not limited to the following examples:

- Limited functional status as indicated by an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2
- Significant comorbidity (e.g., severe cardiac, pulmonary or renal disease)
- AML without favorable cytogenetics or molecular markers
- AML secondary to prior antineoplastic therapy
- AML preceded by a hematologic disorder such as myelodysplastic syndrome

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| CLL and SLL | Venclexta 5-week dose ramp-up schedule:<br>20 mg PO QD for one week followed by 50 mg PO QD for one week, 100 mg PO QD for one week, 200 mg PO QD for one week, then 400 mg PO QD<br><br>Venclexta in combination with Gazyva:<br>On Cycle 1 Day 22, start Venclexta according to the 5-week ramp-up schedule. Continue Venclexta 400 mg QD from Cycle 3 Day 1 until the last day of Cycle 12.<br><br>Venclexta in combination with rituximab:<br>Administer rituximab after the 5-week ramp-up schedule with Venclexta. Continue Venclexta 400 mg QD for 24 months from Cycle 1 Day 1 of rituximab.<br><br>Venclexta as monotherapy:<br>400 mg PO QD after the patient has completed the 5-week dose ramp-up schedule until disease progression or unacceptable toxicity | 400 mg/day |
| AML | PO QD in combination with azacitidine, decitabine, or low-dose cytarabine:<br>• Day 1: 100 mg/day<br>• Day 2: 200 mg/day<br>• Day 3: 400 mg/day<br>• Day 4 and beyond, until disease progression or unacceptable toxicity:<br>  ○ In combination with azacitidine or decitabine: 400 mg/day<br>  ○ In combination with low-dose cytarabine: 600 mg/day | 400 mg/day with azacitidine or decitabine; 600 mg/day with cytarabine |

## VI. Product Availability

Tablets: 10 mg, 50 mg, 100 mg

## VII. References

1. Venclexta Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2022. Available at: https://www.venclexta.com. Accessed August 2, 2022.

2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 2, 2022.
3. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymophoma Version 3.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed August 2, 2022.
4. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed August 2, 2022.
5. National Comprehensive Cancer Network. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed August 2, 2022.
6. National Comprehensive Cancer Network. Systemic Light Chain Amyloidosis Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf. Accessed August 2, 2022.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created: adapted from CP.CPA.294 (to be retired); added Medicaid, new criteria added for new FDA indication: CLL or SLL, with our without 17p deletion; new policy for Medicaid line of business; added prescriber and age requirements; removed confirmation of the presence of 17p deletion per updated FDA labeling; added continuation of care language for CLL/SLL under continued therapy section; references reviewed and updated. | 07.17.18 | 08.18 |
| 4Q 2018 annual review: added off-label coverage criteria for mantle cell lymphoma (NCCN category 2A recommendation); references reviewed and updated. | 08.07.18 | 11.18 |
| Criteria added for new FDA indication: AML; references reviewed and updated. | 01.08.19 | 02.19 |
| Clarified that prior authorization may be required for the agents for prior and combination therapy in I.A.4, 1.B.4, and 1.C.5. | 04.22.19 | |
| CLL/SLL criteria updated to allow use as first-line therapy in combination with Gazyva consistent with the expanded FDA indication; references reviewed and updated. | 06.11.19 | 08.19 |
| 4Q 2019 annual review: CLL/SLL monotherapy or combination therapy with rituximab added in the subsequent therapy setting; AML NCCN alternative uses for relapse/refractory disease and remission added; Appendix B updated to reconcile with similar policies; FDA/NCCN dosing limitation added; references reviewed and updated. | 09.04.19 | 11.19 |
| 4Q 2020 annual review: HIM line of business added; references reviewed and updated. | 08.11.20 | 11.20 |
| 4Q 2021 annual review: revised mantle cell lymphoma to require use as a single agent or in combination with rituximab or ibrutinib | 06.28.21 | 11.21 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| per NCCN; added off-label coverage for BPDCN and multiple myeloma per NCCN; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated. | | |
| 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 |
| 4Q 2022 annual review: for BPDCN, added option of relapsed/refractory disease per NCCN; added criteria for off-label NCCN-supported indications of systemic light chain amyloidosis and Waldenström macroglobulinemia/lymphoplasmacytic lymphoma; added generic oral oncology agent redirection verbiage; references reviewed and updated. Template changes applied to other diagnoses/indications. | 08.02.22 | 11.22 |

**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.

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**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.