Clinical Policy: Venetoclax (Venclexta)

Reference Number: ERX.SPA.253
Effective Date: 07.17.18
Last Review Date: 11.21
Line of Business: Commercial, 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*

  **This indication is approved under accelerated approval based on response rates. 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Venclexta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Lymphocytic Leukemia or 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. 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 for these therapies.*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 400 mg (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:
Commercial – Length of Benefit
Medicaid – 6 months

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. If diagnosis is AML: Member meets 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.*
5. If diagnosis is BPDCN: 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]);
6. Prescribed in combination with azacitidine, decitabine, or low-dose (20 mg/m^2) cytarabine;*
    **Prior authorization may be required.*
7. Request meets one of the following (a, b, or c):*
    a. In combination with azacitidine or decitabine: Dose does not exceed 400 mg (4 tablets) per day;
    b. In combination with low-dose cytarabine: Dose does not exceed 600 mg (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:
Commercial – Length of Benefit
Medicaid – 6 months

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. Member has received ≥ 1 prior therapy (see Appendix B for examples);*
    **Prior authorization may be required.*
5. Prescribed as a single agent or in combination with rituximab or ibrutinib;
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:
Commercial – Length of Benefit
Medicaid – 6 months

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. Member has received ≥ 1 prior therapy (*see Appendix B for examples*);*
    **Prior authorization may be required.*
5. Prescribed in combination with dexamethasone;
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:
Commercial – Length of Benefit
Medicaid – 6 months

E. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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 AML, prescribed in combination with azacitidine, decitabine, or low-dose (20 mg/m^2) cytarabine;*
   **Prior authorization may be required.*
4. 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 400 mg (4 tablets) per day;
   b. In combination with low-dose cytarabine for AML: New dose does not exceed 600 mg (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:
Commercial – Length of Benefit
Medicaid – 12 months

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
CLL/SLL *Examples of first-line, second-line and subsequent therapies:* • FCR (fludarabine, cyclophosphamide, rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• HDMP (high-dose methylprenisolone) + rituximab 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 cytarabine with idarubicin or daunorubicin cytarabine with idarubicin or daunorubicin or mitoxantrone	Age < 60 years: example of intensive induction therapy: cytarabine 100 – 200 mg/m² continuous IV infusion x 7 days with idarubicin 12 mg/m² IV or daunorubicin 60-90 mg/m² IV x 3 days Age ≥ 60 years: example of intensive induction therapy: cytarabine 100 – 200 mg/m² continuous IV infusion x 7 days with idarubicin 12 mg/m² IV or daunorubicin 60-90 mg/m² IV x 3 days or mitoxantrone 12 mg/m² x 3 days	Varies
Mantle cell lymphoma Examples of induction/chemoimmuno therapy: • RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) • Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin)	Varies	Varies
Multiple myeloma Examples of primary therapy: • Bortezomib/cyclophosphamide or lenalidomide/dexamethasone • Carfilzomib or ixazomib/lenalidomide/ dexamethasone • Daratumumab/lenalidomide/ dexamethasone ± bortezomib • Lenalidomide/dexamethasone • Daratumumab/bortezomib/ mephalan/prednisone • Daratumumab/cyclophosphamide /bortezomib/dexamethasone	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of maintenance therapy: • Lenalidomide • Ixazomib • Bortezomib		

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: 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 Venclexta in combination with Gazyva: 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. Venclexta in combination with rituximab: 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. Venclexta as monotherapy: 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:
	• Day 1: 100 mg/day
	• Day 2: 200 mg/day
	• Day 3: 400 mg/day
	• Day 4 and beyond, until disease progression or unacceptable toxicity:
	  ○ In combination with azacitidine or decitabine: 400 mg/day
	  ○ In combination with low-dose cytarabine: 600 mg/day
		400 mg/day with azacitidine or decitabine; 600 mg/day with cytarabine

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VI. Product Availability
Tablets: 10 mg, 50 mg, 100 mg

VII. References
1. Venclexta Prescribing Information. North Chicago, IL: AbbVie Inc.; November 2020. Available at: https://www.venclexta.com. Accessed July 27, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 28, 2021.
3. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymophoma Version 4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 13, 2021.
4. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 15, 2021.
5. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 13, 2021.
6. National Comprehensive Cancer Network. Multiple Myeloma Version 7.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed July 13, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	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.	07.25.18	11.18
Criteria added for new FDA indication: AML; references reviewed and updated.	01.08.19	02.19
CLL/SLL criteria updated to allow use as first-line therapy in combination with Gazyva consistent with the expanded FDA indication; added Medicaid line of business with 6/12 month approval durations; 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 relapsed/refractory disease and remission added; Appendix B updated to reconcile with similar policies; FDA/NCCN dosing limitation added; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	09.04.19	11.19
4Q 2020 annual review: no significant changes; 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 per NCCN; added off-label coverage for BPDCN and multiple myeloma per NCCN; references reviewed and updated.	06.28.21	11.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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