RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	venetoclax
Policy Number:	RxA.617
Drug(s) Applied:	Venclexta®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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

It is indicated:

- For the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- In combination with azacitidine, 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.*

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
venetoclax (Venclexta®)	CLL and SLL	<u>Venclexta® 5-week dose ramp-up schedule:</u> 20 mg orally once daily for one week followed by 50 mg orally once daily for one week, 100 mg orally once daily for one week, 200 mg orally once daily for one week, then 400 mg orally once daily. <u>Venclexta® in combination with obinutuzumab:</u> On Cycle 1 Day 22, start Venclexta® according to the 5-week ramp-up schedule. Continue Venclexta® 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. <u>Venclexta® in combination with rituximab:</u>	400 mg/day

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Administer rituximab after the 5-week ramp-up schedule with Venclexta®. Continue Venclexta® 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab. <u>Venclexta® as monotherapy:</u> 400 mg orally once daily after the patient has completed the 5-week dose ramp-up schedule until disease progression or unacceptable toxicity	
	AML	Orally once daily 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

Dosage Forms

- Tablets: 10 mg, 50 mg, 100 mg

Clinical Policy

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

I. Initial Approval Criteria

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

1. Diagnosis of CLL or SLL;
2. Request is for one of the following (a or b);
   a. Without del(17p)/TP53 mutation in frail patients with significant comorbidity (not able to tolerate purine analogs) or age ≥ 65 years and younger patients with or without significant comorbidities;
   b. With del(17)p/TP53 mutation;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Request meets one of the following (a or b):*
   a. Prescribed in combination with Gazyva® as first-line therapy;

b. Meets (i and ii):
   i. Prescribed as monotherapy or in combination with rituximab;
   ii. Disease is relapsed or refractory after at least one prior therapy (*see examples of prior therapy at Appendix B*);

**Prior authorization may be required.*

6. Request meets one of the following (a or b):*
   c. Dose does not exceed 400 mg (4 tablets) per day;
   d. 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: 6 months
Medicaid: 6 months

B. Acute Myeloid Leukemia (must meet all)**:**
1. Diagnosis of AML;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. 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. Prescribed in combination with azacitidine, decitabine, or low-dose (20 mg/m^2) cytarabine;*
   **Prior authorization may be required.*
6. 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: 6 months
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. 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: 6 months
Medicaid: 6 months

D. Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) AML (must meet all)**:**
1. Diagnosis of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) AML;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Request is for one of the following (a or b);
   a. Systemic disease treated with palliative intent (patients with low performance and/or nutritional status (ie, serum albumin <3.2 g/dL; not a candidate for intensive remission therapy or tagraxofusp-erzs);
   b. Relapsed/refractory disease;
5. 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: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication that has been authorized by RxAdvance, 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: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AML: Acute myeloid leukemia
BCL-2: B-cell lymphoma 2 protein
CLL: Chronic lymphocytic leukemia
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
SLL: Small lymphocytic lymphoma

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
CLL/SLL *Examples of first-line, second-line and subsequent therapies:* • FCR (fludarabine, cyclophosphamide, rituximab) • 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	Varies	Varies
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/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 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 Examples of induction/chemoimmuno therapy: • RDHA (rituximab, dexamethasone, cytarabine) + platinum therapy (e.g., carboplatin, cisplatin, oxaliplatin) • Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin)	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

References

1. Venclexta® Prescribing Information. North Chicago, IL: AbbVie Inc.; May 2020. Available at: https://www.venclexta.com. Accessed August 28 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed September 4, 2019.
3. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymophoma Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed October 13 28 2020.
4. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf Accessed October 13 28 2020.
5. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf . Accessed August 28 2020. .

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	03/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title table was updated. 2. Commercial approval duration was updated for initial approval criteria from “length of benefit” to “6 months”. 3. Commercial approval duration was updated for continued approval criteria from “length of benefit” to “12 months”. 4. Initial Approval criteria I.A.2 added. 5. Off label indication Added: Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) AML	12/03/2020	12/07/2020

6. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by Rxadvance…”. 7. APPENDIX B: Therapeutic Alternatives statement was rephrased to “Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements”. 8. References were reviewed and updated.		