LifeWise Assurance Company

PHARMACY POLICY – 5.01.568

Venclexta (venetoclax) BCL-2 Inhibitor

Effective Date:	Apr. 1, 2025
Last Revised:	Mar. 24, 2025
Replaces:	N/A

RELATED MEDICAL POLICIES:

5.01.534	Multiple Receptor Tyrosine Kinase Inhibitors
5.01.607	Continuity of Coverage for Maintenance Medications
8.01.503	Immune Globulin Therapy

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Introduction

In the simplest terms, cancer is the growth of too many cells. Cells have a normal cycle. New cells are created, they mature and fulfill specialized functions, and then die. The cycle starts over again with new, healthy cells. In cancer, however, the old or damaged cells don't die. Instead, they keep duplicating. Unlike healthy cells, cancer cells don't have any specialized function. That's one reason why they can dodge the immune system to keep growing. Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and acute myeloid leukemia (AML) are cancers of specific types of blood cells. Venclexta (venetoclax) works by targeting the build-up of a naturally occurring protein. Too much of this protein, known as BCL-2, prevents the CLL, SLL, and AML cancer cells from dying. By zeroing in and attaching to this protein, Venclexta helps restore the natural cycle of cell death. Returning to the natural cell cycle reduces the number of cancer cells. This policy explains when Venclexta may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

Policy Coverage Criteria

Condition	Medical Necessity
Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)	**Venclexta (venetoclax) may be considered medically necessary for the treatment of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) when:** • The individual is aged 18 years or older **AND** • Diagnosed with CLL or SLL
Acute Myeloid Leukemia (AML)	**Venclexta (venetoclax) may be considered medically necessary for the treatment of adults with newly-diagnosed acute myeloid leukemia (AML) when:** • Used in combination with azacitidine or decitabine or low-dose cytarabine **AND** • The individual is aged 75 years or older **OR** • Has comorbidities that preclude use of intensive induction chemotherapy

Drug	Investigational
Venclexta (venetoclax)	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Venclexta (venetoclax) not outlined in the Medical Necessity section above is considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for all drugs listed in the policy may be approved up to 3 months.**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and response to therapy (for re-authorization)

Coding

N/A

Related Information

Benefit Application

Venclexta (venetoclax) is managed through the pharmacy benefit.

Definition of Terms

17p deletion: The shorter arm part of chromosome #17 is designated as "p" and is missing in a cell with 17p deletion.

BCL-2: An anti-apoptotic protein (it inhibits programmed cell death and stops the system from destroying non-functional/malignant cells) that is commonly overexpressed in some cancers,

including CLL. Thus, the use of a BCL-2 inhibitor is thought to help counteract the action of this protein.

Evidence Review

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

Venclexta is an oral agent indicated for the treatment of individuals with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by a FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate.

Venclexta is also FDA approved when used 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.

Summary of Evidence

The efficacy of Venclexta was established in an open-label, single-arm, multicenter clinical trial of 106 individuals with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from individuals using Vysis CLL FISH Probe Kit, which is FDA approved for selection of individuals for Venclexta treatment. Individuals received Venclexta via a weekly ramp-up schedule starting at 20mg and ramping to 50mg, 100mg, 200mg, and finally 400mg once daily. Individuals continued to receive 400mg of Venclexta orally once daily until disease progression or unacceptable toxicity.

The efficacy of Venclexta was evaluated by overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic

Lymphocytic Leukemia (IWLCC) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Table 1 summarizes the baseline demographic and disease characteristics of the study population.

Table 1. Baseline Individual Characteristics

Characteristics	N=106
Age, years; median (range)	67 (37-83)
White, %	97.1
Male, %	65.1
ECOG performance status, %	
0	39.6
1	51.9
2	8.5
Tumor burden, %	
Absolute lymphocyte count ≥25x 109 / L	50.0
One or more nodes ≥5 cm	52.8
Number of prior therapies, median (range)	2.5 (1-10)
Time since diagnosis; months, median (range)[a]	79.4 (1.2-385.6)

[a]N=105

The median time on treatment of the time of evaluation was 12.1 months (range: 0 to 21.5 months). Efficacy results are shown in **Table 2**.

Table 2. Efficacy Results for Individuals with Previously Treated CLL with 17p Deletion by IRC

	Venclexta, N=106
ORR, n (%)	85 (80.2)
(95% CI)	(71.3, 87.3)

	Venclexta, N=106
CR + CRi, n (%)	8 (7.5)
CR, n (%)	6 (5.7)
CRi, n (%)	2 (1.9)
nPR, n (%)	2 (2.8)
PR, n (%)	74 (69.8)

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission

The median time to first response was 0.8 months (range: 0.1 to 8.1 months). Median duration of response (DOR) has not been reached with approximately 12 months median follow-up. The DOR ranged from 2.9 to 19.0+ months.

Minimal residual disease (MRD) was evaluated in peripheral blood and bone marrow for individuals who achieved CR or CRi, following treatment with Venclexta. Three percent (3/106) were MRD negative in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes).

The safety of single agent Venclexta at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data of 240 individuals with previously treated CLL from two phase 2 trials and one phase 1 trial. In the pooled dataset, the median age was 66 years (range: 29 to 85 years), 95% were white, and 69% were male. The median number of prior therapies was 3 (range: 1 to 12). The median duration of treatment with Venclexta at the time of data analysis was approximately 10.3 months (range: 0 to 34.1 months). Approximately 46% of individuals received Venclexta for more than 48 weeks. The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Serious adverse reactions were reported in 43.8% of individuals. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and TLS.

Discontinuations due to adverse reactions occurred in 8.3% of individuals. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA. Dosage adjustments due to adverse reactions occurred in 9.6% of individuals. The most frequent adverse reactions leading to dose adjustments were neutropenia, febrile neutropenia, and thrombocytopenia.

The NCCN recommendation of venetoclax monotherapy in relapsed/refractory CLL regardless of 17p status was based on a phase 2 trial involving 91 CLL individuals previously treated with ibrutinib. This non-randomized, open-label trial did not exclude individuals without 17p deletion. However, over 75% of the participants had either a 17p deletion or a TP53 mutation. The interim analysis showed a 65% response rate to venetoclax monotherapy. A similar study with 36 CLL individuals who progressed during or after idelalisib therapy showed an overall response rate of 67% to venetoclax monotherapy. The estimated 12-month PFS rate was 79% for individuals with CLL refractory to or relapsed after treatment with idelalisib. The most common grade 3-4 adverse events were neutropenia (50%), thrombocytopenia (25%), and anemia (17%).

The efficacy of venetoclax plus rituximab in individuals with relapsed/refractory CLL was established in a randomized, open-label, phase III trial with 389 individuals. The MURANO trial used an active comparator as control: a regimen of bendamustine and rituximab. Individuals were randomized to receive either 6 months of venetoclax plus rituximab or bendamustine plus rituximab. After a median follow-up of 23.8 months, the overall response rate (93.3% vs 67.7%; $P < 0.0001$), CR rate (26.8% vs 8.2%; $P < 0.0001$), the median PFS (not reached vs. 17 months; $P < 0.0001$), and the estimated 24-month PFS rate (84.9% vs 36.3%) were significantly higher for venetoclax plus rituximab than for bendamustine plus rituximab. The superiority of venetoclax-rituximab was maintained across all subgroups, including the subgroup of individuals with 17p deletion. The 24-month PFS rate among individuals with 17p deletion was 81.5% vs 27.8%. The 24-month PFS rate among individuals without 17p deletion was 85.9% vs 41.0%. However, the investigator-assessed CR rate did not agree with independent review committee-assessed CR rate. The ICR-assessed CR rate was 8.2% vs 3.6% ($P = 0.08$).

In the MURANO trial, the incidence of grade 3 - 4 neutropenia (57.7% vs 38.8%) and grade 3 - 4 TLS (3.1% vs 1.1%) were higher with venetoclax plus rituximab. The incidence of grade 3-4 febrile neutropenia (3.6% vs 9.6%), AEs leading to death (5.2% vs 5.9%), and Richter transformation (3.1% vs 2.6%) were not elevated with venetoclax plus rituximab.

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating Venclexta. In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting dose, the incidence of TLS was 12% (9/77; 4 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures. In venetoclax clinical trials, individuals with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 10^9/L and any measurable lymph node ≥5 cm were hospitalized to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the ramp-up phase.

In 66 individuals with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events. The events occurred in individuals who had a lymph node(s) ≥5 cm or ALC ≥25 x 10^9/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, seizures, or sudden death was observed in these individuals. All individuals had CrCl ≥50 mL/min.

Regulatory Information

Continued approval (by the FDA) for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2018 Update

A literature search from 1/1/2017 to 4/16/18 was performed, including review of the current NCCN guidelines. Updated evidence summary. Added criteria for reauthorization after three months.

2019 Update

Reviewed Venclexta (venetoclax) prescribing information and no additional FDA-approved indications were identified that would impact this policy.

2020 Update

Reviewed Venclexta (venetoclax) prescribing information and no additional FDA-approved indications were identified that would impact this policy.

2021 Update

Reviewed Venclexta (venetoclax) prescribing information and no additional FDA-approved indications were identified that would impact this policy.

2022 Update

Reviewed Venclexta (venetoclax) prescribing information. The prescribing information was updated in June 2022 to list that the CLL/SLL Starting Pack provides the first 4 weeks of Venclexta according to the ramp-up schedule. No information was identified that would impact the policy statements.

2023 Update

Reviewed prescribing information of Venclexta. No new evidence found that would change the policy statements.

2024 Update

Reviewed prescribing information of Venclexta. No new evidence found that would change the policy statements.

2025 Update

Reviewed prescribing information of Venclexta. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

References

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History

Date	Comments
07/01/16	New policy, add to Prescription Drug section, approved June 14, 2016. Venclexta® may be considered medically necessary to treat patients with CLL when criteria are met; investigational for all other indications.
10/01/16	Interim Update, changes approved September 13, 2016. Minor language update of the criteria section.
05/01/17	Annual Review, changes approved April 11, 2017. A statement outlining the length of therapy for initial and subsequent approval has been added to the policy.
06/01/18	Annual Review, approved May 3, 2018. A literature search from 1/1/2017 to 4/16/18 was performed. Updated evidence summary. Added criteria for reauthorization after three months. Removed oral drug HCPCS code J8499.
07/01/18	Interim Review, approved June 22, 2018. Criteria was updated to reflect prescribing information update. Benefit application and length of approval sections were added.
02/01/19	Interim Review, approved January 8, 2019. Added Venclexta® indication for the treatment of AML.
05/01/19	Annual Review, approved April 18, 2019. No changes to policy statements.
08/01/19	Interim Review, approved July 25, 2019. Updated criteria for CLL and SLL indications removing the requirement to try one prior therapy.
08/01/20	Annual Review, approved July 23, 2020. No changes to policy statements.
10/01/21	Annual Review, approved September 23, 2021. No changes to policy statements.
12/01/22	Annual Review, approved November 21, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
10/01/23	Annual Review, approved September 11, 2023. No changes to policy statements.
06/01/24	Annual Review, approved May 24, 2024. No changes to policy statements.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). **Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.