PREMERA HMO

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PHARMACY POLICY – 5.01.568

BCL-2 Inhibitors

Effective Date:	Nov. 1, 2026
Last Revised:	Oct. 13, 2026
Replaces:	N/A

RELATED MEDICAL POLICIES:

5.01.534	Multiple Receptor Tyrosine Kinase Inhibitors
5.01.590	Bruton 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. Healthy cells follow a natural life cycle: they are created, carry out their jobs, and eventually die so new cells can take their place. Cancer happens when this process breaks down. Damaged cells continue to survive and multiply instead of dying, leading to an increasing number of abnormal cells that can grow uncontrollably and sometimes evade the body's immune system. Unlike healthy cells, cancer cells do not have any specialized function. That is one reason why they can dodge the immune system to keep growing. BCL-2 inhibitors work by blocking a protein called BCL-2, which helps cancer cells stay alive longer than they should. By blocking this protein, these medications remove the cancer cells' "survival signal" and allow the body's natural process for getting rid of damaged or abnormal cells to restart. This causes the cancer cells to self-destruct and die, which can help slow or stop the growth of the cancer. This policy explains when Beqalzi (sonrotoclax) and Venclexta (venetoclax) 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
Beqalzi (sonrotoclax)	**Beqalzi (sonrotoclax) may be considered medically necessary for the treatment of adult individuals with relapsed or refractory mantle cell lymphoma (MCL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with relapsed or refractory MCL **AND** • Has received at least 2 lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (e.g., acalabrutinib, zanubrutinib) **AND** • The dose is limited to 320 mg once daily
Venclexta (venetoclax)	**Venclexta (venetoclax) may be considered medically necessary for the treatment of individuals with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Diagnosed with CLL or SLL **Venclexta (venetoclax) may be considered medically necessary for the treatment of adult individuals with newly-diagnosed acute myeloid leukemia (AML) when the following criteria are met:** • The individual meets 1 of the following: o Is aged 75 years or older **OR** o Has comorbidities that preclude use of intensive induction chemotherapy **AND** • Has newly-diagnosed AML **AND**

	• Medication is used in combination with azacitidine, decitabine, low-dose cytarabine, or Inqovi (decitabine and cedazuridine)

Drug	Investigational
• **Beqalzi (sonrotoclax)** • **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 Beqalzi (sonrotoclax) and Venclexta (venetoclax) not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in this policy may be approved up to 6 months.**
Re-authorization criteria	**All drugs listed in this policy may be approved up to 12 months when the drug-specific coverage criteria are met and there is evidence 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 medication history

Coding

N/A

Related Information

Benefit Application

Beqalzi (sonrotoclax) and Venclexta (venetoclax) are 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

Beqalzi (sonrotoclax)

Beqalzi is an inhibitor of BCL-2 protein. Overexpression of BCL-2 in various cancers mediates cell survival and has been associated with chemotherapeutic resistance. Beqalzi binds to the BCL-2 protein, displacing pro-apoptotic proteins, thereby inducing apoptosis of cells. In nonclinical studies, sonrotoclax demonstrated cytotoxicity in cancer cells overexpressing BCL-2, with a series of intrinsic apoptotic events, including caspase activation.

Beqalzi is indicated for the treatment of adult individuals with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor. The efficacy was evaluated in a single-arm, multicenter clinical trial, BGB-11417 201 (NCT05471843). Efficacy was based on 103 adults with relapsed or refractory MCL who previously received anti-CD20–based therapy and a BTK inhibitor. The trial required an ANC ≥1000/mm3, platelets ≥75,000/mm3, and AST and ALT ≤3 × upper limit of normal (ULN). The trial excluded individuals with central nervous system lymphoma, prior BCL-2 inhibitor, or an ECOG performance status >2. Following completion of the ramp-up dosing schedule, individuals received Beqalzi at 320 mg orally once daily. The median age was 68 years (range: 39 to 85 years); 74% were male; 58% were White, 33% Asian, and 3% Black or African American. Most

individuals (93%) had an ECOG performance of 0 to 1. Individuals had a median of 3 prior lines of therapy (range: 1 to 8), with 89% having at least 2 and 60% having at least 3 prior lines of therapy. All individuals were exposed to at least one covalent or noncovalent BTK inhibitor, most commonly ibrutinib (53%), zanubrutinib (27%), and pirtobrutinib (14%). Other prior therapies included lenalidomide in 19%, autologous HSCT in 17%, and CAR-T therapy in 2%. The simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) score was low in 35%, intermediate in 36%, and high in 29% of individuals. High (≥30%) Ki-67 expression was detected in 35% of individuals. Efficacy was established based on overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee (IRC) using 2014 Lugano criteria. Results demonstrated an overall response rate of 52% with a median time to response of 1.9 months (range: 1.6 to 6.2). The median duration of response was 15.8 months.

Beqalzi's label includes specific warnings regarding tumor lysis syndrome (TLS), serious infections, and neutropenia. To mitigate the risk of TLS, the recommended dosage begins with a 4-week ramp-up phase, followed by a daily oral dose of 320 mg. Clinically relevant adverse reactions in < 10% of individuals who received Beqalzi included: TLS, headache, nausea, vomiting, mucositis, peripheral sensory neuropathy, febrile neutropenia, pneumonitis, herpes zoster infection, and sepsis.

Venclexta (venetoclax)

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 an 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).

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.

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.

2026 Update

Reviewed prescribing information of Venclexta. Updated initial authorization for all other reviews for all drugs listed in the policy from 3 months to 6 months.

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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.
05/01/26	Annual Review, approved April 13, 2026. Updated initial authorization for all other reviews for all drugs listed in the policy from 3 months to 6 months.
11/01/26	Interim Review, approved October 13, 2026. Updated policy title from 5.01.568 Venclexta (venetoclax) BCL-2 Inhibitor to 5.01.568 BCL-2 Inhibitors. Added coverage

Date	Comments
	criteria for Beqalzi (sonrotoclax) for the treatment of relapsed or refractory MCL. Updated criteria for Venclexta (venetoclax) and treatment of newly-diagnosed AML adding Inqovi (decitabine and cedazuridine) to list of medications it may be used in combination with. Removed reference to non-formulary exception reviews. Added 5.01.590 Bruton Tyrosine Kinase Inhibitors to Related Medical Policies.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit 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). ©2026

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