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.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)</strong></td>
<td>Venclexta® (venetoclax) may be considered medically necessary for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.</td>
</tr>
</tbody>
</table>
| **Acute Myeloid Leukemia (AML)**               | Venclexta® (venetoclax) may be considered medically necessary for the treatment of newly-diagnosed acute myeloid leukemia (AML) when:  
  - Used in combination with azacitidine or decitabine or low-dose cytarabine  
  AND  
  - Patient is age 75 years or older  
  OR  
  - Has comorbidities that preclude use of intensive induction chemotherapy |

<table>
<thead>
<tr>
<th><strong>Length of Approval</strong></th>
<th><strong>Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval: All oral oncology drugs, unless otherwise specified</strong></td>
<td>Initial approval for three months, according to the medical necessity criteria specified for each drug.</td>
</tr>
<tr>
<td><strong>Reauthorization</strong></td>
<td>Continued therapy will be approved for periods of one year as long as the drug-specific conditions are met, and the patient has shown and continues to show clinical benefit.</td>
</tr>
</tbody>
</table>
| **Documentation**                               | **Initial:** Chart notes demonstrating that the patient meets the stated criteria for medical necessity.  
  **Reauthorization:** Chart notes demonstrating that the patient continues to show clinical benefit. |

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Investigational</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venclexta® (venetoclax)</strong></td>
<td>All uses of Venclexta® (venetoclax) not outlined in the Medical Necessity section above are considered</td>
</tr>
<tr>
<td>Drug</td>
<td>Investigational</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>investigational.</td>
</tr>
</tbody>
</table>

**Coding**

N/A

**Related Information**

**Benefit Application**

The drugs included in this policy 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. The only approved FDA test for 17p deletion is Vysis CLL FISH Prole Kit, which detects the deletion of the LSI TP53 probe target. LSI TP53 covers the 17p13.1 region where the TP53 gene is located. TP53 encodes for the tumor suppressor p53. The p53 protein plays a role in determining whether a cell with damaged DNA will undergo DNA repair or apoptosis (programmed cell death). By recognizing and eliminating mutated cells, p53 prevents tumor formation.

**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 patients 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 with or without rituximab is recommended by NCCN in treating relapsed/refractory CLL with or without 17p deletion.

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 patients 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 patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for Venclexta treatment. Patients received Venclexta via a weekly ramp-up schedule starting at 20mg and ramping to 50mg, 100mg, 200mg, and finally 400mg once daily. Patients 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 Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>67 (37-83)</td>
</tr>
<tr>
<td>White, %</td>
<td>97.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>65.1</td>
</tr>
<tr>
<td>ECOG performance status, %</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39.6</td>
</tr>
<tr>
<td>1</td>
<td>51.9</td>
</tr>
<tr>
<td>2</td>
<td>8.5</td>
</tr>
<tr>
<td>Tumor burden, %</td>
<td></td>
</tr>
<tr>
<td>Absolute lymphocyte count ≥25x10^9/L</td>
<td>50.0</td>
</tr>
<tr>
<td>One or more nodes ≥5 cm</td>
<td>52.8</td>
</tr>
<tr>
<td>Number of prior therapies, median (range)</td>
<td>2.5 (1-10)</td>
</tr>
<tr>
<td>Time since diagnosis; months, median (range)^a</td>
<td>79.4 (1.2-385.6)</td>
</tr>
</tbody>
</table>

^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 Patients with Previously Treated CLL with 17p Deletion by IRC

<table>
<thead>
<tr>
<th></th>
<th>Venclexta®, N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>85 (80.2)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(71.3, 87.3)</td>
</tr>
<tr>
<td>CR + CRi, n (%)</td>
<td>8 (7.5)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>CRi, n (%)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>nPR, n (%)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>74 (69.8)</td>
</tr>
</tbody>
</table>
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 patients 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 patients 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 patients 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 patients. 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 patients. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA. Dosage adjustments due to adverse reactions occurred in 9.6% of patients. 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 patients previously treated with ibrutinib. This non-randomized, open-label trial did not exclude patients 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 patients 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 patients 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 patients with relapsed/refractory CLL was established in a randomized, open-label, phase III trial with 389 patients. The MURANO trial used an active comparator as control: a regimen of bendamustine and rituximab. Patients 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 patients with 17p deletion. The 24-month PFS rate among patients with 17p deletion was 81.5% vs 27.8%. The 24-month PFS rate among patients 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 [see Dosage and Administration (2.2, 2.3)]. In venetoclax clinical trials, patients with any measurable lymph node \(\geq 10\) cm or those with both an ALC \(\geq 25 \times 10^9/L\) and any measurable lymph node \(\geq 5\) 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 patients 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 \(\geq 2\) 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 patients who had a lymph node(s) \(\geq 5\) cm or ALC \(\geq 25 \times 10^9/L\).
No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, seizures, or sudden death was observed in these patients. All patients 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.

References


15. California Cancer Registry. Five-Year Incidence and Mortality Counts and Average Annual Age-Specific and Crude Rates per 100,000 Persons by Age, Race/Ethnicity, and Sex, California, 2010-2014, Leukemia: Chronic Lymphocytic.

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/16</td>
<td>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.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Interim Update, changes approved September 13, 2016. Minor language update of the criteria section.</td>
</tr>
<tr>
<td>05/01/17</td>
<td>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.</td>
</tr>
<tr>
<td>06/01/18</td>
<td>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.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Interim Review, approved June 22, 2018. Criteria was updated to reflect prescribing information update. Benefit application and length of approval sections were added.</td>
</tr>
<tr>
<td>02/01/19</td>
<td>Interim Review, approved January 8, 2019. Added Venclexta® indication for the treatment of AML.</td>
</tr>
</tbody>
</table>

**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). ©2019 Premera All Rights Reserved.

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  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi a li a kapab genyen efòmsyon enpòtan konsèn aplan apikasyon lo a nansi konvèsan kouvéti aisyen la atrav Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi a. Ou ka gen pou pouan kék aplan avan saetet limit pou pou ka kente kouvéti aisyen sante w la nansi pou yo ka ede w avèkꕍ repas yo. Se dwa w pou resewa efòmsyon sa a ak aq asistans na lang ou pale a, san ou pa gen pou peye pou sou. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ikloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impomrsyon. Daytoy a pakdaa mabalind nga adda ket naglaon iti napateg nga impomrsyon maipanggep iti apikasyonowo yenno coverage baben a Iti Premera Blue Cross. Daytoy ket mabalind dagiti importante a pelsa iti daytoy a pakdaa. Mabalind nga adda rumbeng nga aramideng nga addang sakbay dagiti partikulor a naituding nga aimal tapo maplagatinaloido ti coverage ti salun-atyo yenno tulong kadagiti gastos. Adda karbenganyo a mangala ti daytoy nga impomrsyon ken tulong ti bukodyo a pagasaaa nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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Premera Blue Cross is a nationally recognized health benefits company with the expertise and commitment to provide customers and employer groups with high-quality and affordable health insurance products and services.

Customers who file claims for services that are covered by insurance will receive a Summary of Benefits and Coverage (SBC) in the mail within 60 days of enrollment. The SBC contains important information about the health insurance plan, including:

- what services are covered
- what services are not covered
- what out-of-pocket costs you may have (e.g., deductibles, co-payments)
- whether there are Networks or service areas where services are covered
- any other information required by law

If you need a Spanish-language version of the SBC, please call 1-800-722-1471 (TTY: 800-842-5357) and ask for assistance.

Customers who need assistance to understand the SBC or this explanation should call 1-800-722-1471 (TTY: 800-842-5357)

To obtain a Spanish-language benefit explanation, please call 1-800-722-1471 (TTY: 800-842-5357) and ask for assistance.

If you have questions about the plan, please call 1-800-722-1471 (TTY: 800-842-5357) and ask for assistance.