Introduction

Chronic lymphocytic leukemia (CLL) is a type of cancer in which bone marrow makes too many white blood cells, called lymphocytes. This is the most common type of leukemia in adults. It often occurs during or after middle age, and rarely occurs in children. Normally, the body makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell, or a lymphoid stem cell. In CLL, too many blood stem cells become abnormal lymphocytes, and do not become healthy white blood cells. The abnormal lymphocytes are then called leukemia cells. The lymphocytes are not able to fight infection very well (which it should do when healthy). Also, as the number of lymphocytes increases in the blood and bone marrow, there is less room for healthy white blood cells, red blood cells, and platelets. This may result in an infection, anemia, and easy bleeding.

Standard treatment options commonly used are:

- Watchful waiting
- Radiation therapy
- Chemotherapy
- Surgery
- Targeted therapy
Other options include chemotherapy with stem cell transplant, biologic therapy, and chimeric antigen receptor (CAR) T-cell therapy, which is a type of immunotherapy.

**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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)</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. All other uses Venclexta® (venetoclax) are considered investigational.</td>
</tr>
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</table>

### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval: All oral oncology drugs, unless otherwise specified</td>
<td>Initial approval for three months, according to the medical necessity criteria specified for each drug.</td>
</tr>
<tr>
<td>Reauthorization</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>
<tr>
<td>Documentation</td>
<td>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.</td>
</tr>
</tbody>
</table>
Drug | Investigational
--- | ---
Venclexta® (venetoclax) | All uses of Venclexta® (venetoclax) not outlined in the Medical Necessity section above are considered investigational.

Coding

N/A

Related Information

Benefit Application

The drugs included in this policy may be covered under 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 Proble 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.
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.

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>

^aN=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>Venclexta®, N=106</th>
<th></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 ≥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 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 ≥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) ≥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 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.

**History**

<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>
</tbody>
</table>

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  - Information written in other languages

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  Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf

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