Venclexta (Venetoclax) First BCL-2 Inhibitor Approved for High-Risk Relapsed Chronic Lymphocytic Leukemia

By Lisa A. Raedler, PhD, RPh, Medical Writer

Chronic lymphocytic leukemia (CLL), a cancer of B-cell lymphocytes, is the most common type of leukemia in adults. According to the American Cancer Society, more than 18,900 Americans were estimated to be diagnosed with CLL in 2016. The incidence of CLL increases significantly among individuals aged ≥50 years, with only a small fraction of people diagnosed in their 30s and 40s. The majority of patients with CLL are diagnosed without symptoms based on routine blood work. As it advances, CLL can cause fatigue, swollen lymph nodes, enlarged spleen, shortness of breath, and infections.

The clinical course of CLL is heterogeneous; although some patients live for decades with no treatment, others have disease that is rapidly aggressive. The 5-year survival rate for patients with CLL (all stages combined) is 82%. For the past several decades, chemoimmunotherapy containing a CD20 antibody (ie, rituximab, obinutuzumab, or ofatumumab) and a cytotoxic agent (ie, fludarabine, cyclophosphamide, or chlorambucil) represented the standard treatment for patients with CLL. These regimens are effective for patients with treatment-naïve CLL, but they are associated with significant immunosuppression and secondary malignancies. Patients with high-risk features, including a deletion in chromosomes 11q and 17p, and TP53 mutations have particularly poor outcomes. Although salvage treatment options are available, only allogeneic stem-cell transplantation represents a potential cure for high-risk patients with relapsed CLL.

Studies reveal that leukemic cells found in the peripheral blood of patients with CLL receive survival and proliferation signals from the microenvironment and from B-cell receptors. This finding prompted the development of tyrosine kinase inhibitors (TKIs) that are directed against the B-cell receptor pathway, including Bruton's tyrosine kinase that has demonstrated substantial clinical efficacy in CLL, and was originally approved by the US Food and Drug Administration (FDA) in February 2014 for CLL and has since received several new indications. Ibrutinib (Imbruvica) is a first-in-class oral selective Bruton's tyrosine kinase inhibitor that has demonstrated substantial efficacy in CLL, and was approved by the FDA Approves First BCL-2 Inhibitor for CLL

On April 11, 2016, the FDA approved venetoclax (Venclexta; Janssen) tablets, a first-in-class BCL-2 inhibitor for the treatment of patients with CLL plus chromosome 17p deletion, as detected by an FDA-approved test (Vysis CLL FISH Probe Kit), who have received at least 1 previous therapy. The FDA used its accelerated approval process based on the overall response rate (ORR) to venetoclax, which was 42% in a single-arm, phase 2 clinical trial of 106 patients with CLL who had chromosome 17p deletion and had received at least 1 previous therapy. Overall, 80.2% of patients who received venetoclax had a complete or partial response.

“The patients now have a new, targeted therapy that inhibits a protein involved in keeping tumor cells alive. For certain patients with CLL who have not had favorable outcomes with other therapies, Venclexta may provide a new option for their specific condition,” said Richard Pazdur, MD, Director of the FDA’s Office of Hematology and Oncology Products.
Mechanism of Action

Venetoclax is a selective small-molecule inhibitor of BCL-2, an antiapoptotic protein. The overexpression of BCL-2 in CLL cells is associated with tumor-cell survival and resistance to chemotherapy. Venetoclax facilitates apoptosis by binding directly to the BCL-2 protein, displacing proapoptotic proteins, and triggering mitochondrial outer-membrane permeabilization and caspase activation.

Dosing and Administration

To receive venetoclax, patients with relapsed or refractory CLL must demonstrate the presence of chromosome 17p deletion in blood specimens. Patients with confirmed chromosome 17p deletion should be assessed for the risk for tumor lysis syndrome.

Venetoclax is dosed according to a weekly titration schedule up to the recommended dose of 400 mg daily (Table 1). This 5-week titration schedule is designed to gradually reduce the tumor burden and to reduce the risk for tumor lysis syndrome.

Patients should take venetoclax tablets with a meal and water at approximately the same time every day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken before swallowing.

Specialty Pharmacy Distributors

Venetoclax is distributed through several specialty pharmacies, including ASD Healthcare, Avella, Biologics, Cardinal Health Specialty Distribution, Diplomat, McKesson Specialty Health, McKesson Plasma and Biologics, Onco360, and Oncology Supply.

Pivotal Clinical Trial

The efficacy of venetoclax was established in an open-label, single-arm, multicenter clinical trial of 106 patients with CLL and chromosome 17p deletion who had received at least 1 previous CLL therapy. The presence of chromosome 17p deletion was confirmed using peripheral blood specimens and the FDA-approved test, Vysis CLL FISH Probe Kit.

Venetoclax was dosed using the 5-week titration schedule starting at 20 mg daily and increasing to 50 mg, 100 mg, 200 mg, and 400 mg once daily. Patients continued to receive venetoclax 400 mg until disease progression or unacceptable toxicity.

The primary efficacy end point was overall response rate as assessed by an independent review committee using the 2008 Modified International Workshop on Chronic Lymphocytic Leukemia’s updated National Cancer Institute–sponsored Working Group guidelines.

After a median treatment of 12 months (range, 0–22 months), the overall response rate was 80.2% (95% confidence interval, 71–87), including a 5.7% complete response, 1.9% complete response with incomplete marrow recovery, 2.8% nodular partial remission, and 69.8% partial remission (Table 2). The median time to first response was 0.8 months (range, 0.1–8.1 months). The median duration of response has not been reached (range, 2.9–19.0+ months).

The 8 patients who had a complete response or a complete response with incomplete marrow recovery were evaluated for minimal residual disease in the peripheral blood and bone marrow; 3 of these patients did not have minimal residual disease (<1 CLL cell per 10^4 leukocytes), accounting for 3% of the 106 patients included in the clinical trial.

Adverse Events

The safety of venetoclax was demonstrated based on pooled data from 3 clinical trials involving 240 patients with previously treated CLL. The patients’ median age was 66 years (range, 29–85 years); the majority were white (95%) and male (69%).

The most common (incidence, ≥20%) adverse reactions of any grade included neutropenia (45%), diarrhea (35%), nausea (33%), anemia (29%), thrombocytopenia (29%), upper respiratory tract infection (22%), and fatigue (21%). Overall, 8% of patients discontinued venetoclax because of adverse reactions, including thrombocytopenia.

### Table 1 Venetoclax Titration Dosing Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily dose, mg</th>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>5+</td>
<td>400</td>
</tr>
</tbody>
</table>

*Source: Venclexta (venetoclax) tablets prescribing information; April 2016.

### Table 2 Response Rates with Venetoclax in Patients with CLL

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Venetoclax, N (%) (N = 106)</th>
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<tbody>
<tr>
<td>Overall response rate</td>
<td>85 (80.2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Complete response with incomplete marrow recovery</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Nodular partial remission</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>74 (69.8)</td>
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</table>

*Assessed by an independent review committee.

CI indicates confidence interval; CLL, chronic lymphocytic leukemia.

*Source: Venclexta (venetoclax) tablets prescribing information; April 2016.*

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and autoimmune hemolytic anemia.\textsuperscript{13} Dosage adjustment because of adverse reactions was required in 10% of patients, and was most often secondary to neutropenia, febrile neutropenia, and thrombocytopenia.\textsuperscript{13}

**Contraindications**

The concomitant use of venetoclax with strong cytochrome P3A inhibitors is contraindicated during treatment initiation and during the 5-week titration period.\textsuperscript{13}

**Warnings and Precautions**

Fatal events and renal failure requiring dialysis have occurred with venetoclax therapy. Changes in blood chemistries that require prompt intervention can occur 6 to 8 hours after the first dose of venetoclax and after each dose increase. Prophylactic hydration and antihyperuricemics should be administered before the first dose of venetoclax to reduce the risk for tumor lysis syndrome.\textsuperscript{13}

Patients with reduced renal function are at an increased risk for tumor lysis syndrome, and require intensive monitoring when starting venetoclax therapy.\textsuperscript{13}

Grade 3 or 4 neutropenia has been reported with venetoclax therapy. Complete blood counts should be monitored throughout treatment with venetoclax.\textsuperscript{13}

Venetoclax may cause fatal harm. Females of reproductive potential should use effective contraception during treatment with venetoclax and for at least 30 days after the last dose of venetoclax. Male fertility may be compromised with venetoclax therapy.\textsuperscript{13}

No dose adjustment is needed for patients with mild or moderate renal impairment, and a recommended dose has not been determined for patients with severe renal impairment or for patients receiving dialysis.\textsuperscript{13}

Nursing during treatment with venetoclax is not recommended.\textsuperscript{13} Venetoclax has not been studied in children.\textsuperscript{13}

Dose adjustment is not necessary for patients with mild or moderate hepatic impairment, but monitoring during the initiation and titration of venetoclax is advisable. A recommended dose of venetoclax for patients with severe hepatic impairment has not been determined.\textsuperscript{13}

Live attenuated vaccines should not be administered before, during, or after treatment with venetoclax until B-cell recovery occurs.\textsuperscript{13}

**Conclusion**

Venetoclax is the first BCL-2 inhibitor approved by the FDA for the treatment of patients with relapsed, high-risk CLL. Venetoclax is associated with high response rates, including complete responses without minimal residual disease. The median duration of response with venetoclax has not yet been reached after approximately 12 months of follow-up.

To mitigate the risk for tumor lysis syndrome with venetoclax, a 5-week dose titration schedule has been established. Premedication with antihyperuricemics and adequate hydration are recommended for all patients who start using venetoclax.

Venetoclax’s mechanism of action suggests that combinations or sequencing with other novel targeted agents may improve outcomes for patients with high-risk CLL. Researchers are evaluating the activity of venetoclax monotherapy and venetoclax-based combination therapies in patients with high-risk and standard-risk CLL, as well as in other leukemias and lymphoid malignancies.\textsuperscript{16}