Venetoclax Fact Sheet

(ven ET oh klax)

Generic Name: Venetoclax

Synonyms: ABT-199, GDC-0199, RG7601

Trade Name(s): Venclexta™, Venclexto™, Venclyxto™

Drug Type:
Venetoclax is a targeted therapy, an antineoplastic agent, and a BCL-2 (B cell lymphoma-2) antagonist (for a more detailed explanation, see **How Venetoclax Works** below). To learn more about targeted therapies and pathway inhibitors to B cell signaling, go to https://iwmf.com/publications/ for the IWMF Treatment Options Guide that includes explanations of these drugs.

How Venetoclax Works, and What Conditions Are Treated by This Drug:
Each type of targeted therapy is a little different, but all interfere with the ability of the cancer cell to grow, divide, repair, die, and/or communicate with other cells. Researchers identify specific features of cancer cells that are different from normal cells. This information is used to create a targeted therapy that attacks cancer cells with minimal or no damage to normal cells, thus leading to fewer side effects.

Normal cells live for a certain amount of time and then die by a process called apoptosis. Normal apoptosis ensures that the total number of cells ("the population") will be the right amount and that there won't be too many cells. In some cancers, cell death (apoptosis) is delayed. If cancer cells don't die at the right time, the body cannot get rid of them. The result is too many cancer cells.

Cell death (apoptosis) is a delicate balance. You don't want too much or too little. To best regulate the right level of cell death, normal cells have regulatory proteins that increase cell death and other regulatory proteins that decrease cell death. These regulatory proteins have to be present in just the right amount. One of the normal cell proteins that decreases cell death (apoptosis) is BCL-2. When there is too much BCL-2, cell death is decreased, and the result is too many cells.

In some cancers, including WM, the cancer cells have too much BCL-2. The excess of BCL-2 causes a decrease in cell death, resulting in an excessively large population of WM cells. If BCL-2 could be reduced or inactivated, the right level of cell death could be restored, and the large population of WM cells could be reduced.

Venetoclax is a small molecule targeted therapy that antagonizes BCL-2, thus restoring and promoting apoptosis (cell death) of the WM cells. Venetoclax can get into the WM cell and bind to BCL-2, an anti-apoptotic protein. By blocking BCL-2, venetoclax restores normal apoptosis (death) of the cancer cells.

Several studies have demonstrated that BCL-2 is overexpressed in both B-cells and plasma cells in WM patients in comparison to healthy patients. Furthermore, this overexpression of BCL-2 in patients with WM happens regardless of MYD88 or CXCR4 mutation status, suggesting an independent pathophysiologic mechanism.

Venetoclax Fact Sheet

Venetoclax has US Food and Drug Administration (FDA) approval for the treatment of patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and acute myelogenous leukemia (AML). It should be noted that if a drug has been approved for one use, physicians may elect to use this same drug for other problems if they believe it may be helpful. This is called using a drug "off-label," and clinical trials are ongoing with venetoclax alone and in combination with ibrutinib for patients with WM.

Many treatments used for WM, such as rituximab, bortezomib, carfilzomib, and bendamustine, do not have formal FDA approval for WM. However, the use of these therapies is supported by prospective data, fully vetted, published in peer-reviewed journals, and included as part of the National Comprehensive Cancer Network® (NCCN®) guidelines and the International Waldenstrom's Macroglobulinemia Workshop consensus panel guidelines. Although it is not categorized as a preferred regimen in the NCCN® Guidelines, venetoclax is listed as one of the other recommended regimens for previously treated patients with WM (NCCN Guidelines, version 2.2022, December 7, 2021).

Venetoclax has been studied in a multicenter, prospective Phase 2 trial of relapsed/refractory WM, where it has shown promising results, with an overall response rate of 84%, a major response rate of 81%, and a very good partial response rate of 19%. The major response rate was lower in refractory versus relapsed disease (50% vs. 95%). The median follow-up time was 33 months, and the progression-free survival was 30 months. (For definitions of these response categories go to https://onlinelibrary.wiley.com/doi/10.1111/bjh.12102). Notably, CXCR4 mutations—which can reduce the response to ibrutinib—did not affect treatment response or progression-free survival. The only recurring severe and undesirable side effect was neutropenia, the presence of a lower-than-normal number of neutrophils (45%). A neutrophil is a type of white blood cell that helps fight bacterial infection. This side effect included one episode of febrile neutropenia, marked by fever along with neutropenia. No deaths were reported among the 32 patients over the course of the study. At the halfway point in this clinical trial, venetoclax was found to be an active and tolerable therapy in patients with previously treated WM, regardless of previous exposure to BTK inhibitors, such as ibrutinib, acalabrutinib, or zanubrutinib. There were no episodes of clinical tumor lysis syndrome (see explanation below under **Venetoclax Side Effects**), immunoglobulin M flare, neuropathy, secondary cancers, or cardiac arrhythmias (a condition in which the heart beats with an irregular or abnormal rhythm) associated with venetoclax therapy.

Based on promising results seen with the combination of ibrutinib and venetoclax in CLL patients, a Phase 2 study using this combination in treatment naive WM patients with the MYD88 mutation has begun. Both drugs are being administered for a fixed duration of two years, with four years of follow-up. The hoped-for outcome is that this combination will eliminate the majority of malignant cells in the bone marrow and result in a treatment response that may allow patients to have a prolonged treatment break. Second generation BCL-2 inhibitors are now in development.

How Venetoclax Is Given:
Venetoclax as a monotherapy (one drug) is given in increasing doses, up to 800 mg once daily for previously treated patients with WM. It is a tablet, taken by mouth, with a peak concentration at 5-8 hours after ingestion. These tablets should be swallowed whole once daily with water at mealtimes, as food increases bioavailability. The dose of venetoclax is administered in increasing doses over several weeks to minimize potential side effects. Venetoclax is supplied as 10 mg, 50 mg, and 100 mg tablets. The tablets should not be crushed, cut, or dissolved in water, as this may reduce the venetoclax plasma concentration by up to 50%. They should be stored at room temperature. The dosage should not be changed or stopped by the patient without physician advice. The dose should be taken at approximately the same time each day. If a dose is missed by less than eight hours, take the missed dose of venetoclax right away, then take the next dose as usual. If a dose of venetoclax has been missed and it has been more than eight hours, wait (don't take the venetoclax) and take the next dose of venetoclax at the usual time. Do not take more than one dose of venetoclax in any given day. Call your health care professional, a poison control center, or emergency room right away if too much is taken at one time. **Do not drink grapefruit juice, eat grapefruit, Seville oranges (often used in marmalades), or starfruit while you are taking venetoclax. These foods may increase the amount of venetoclax in your blood.** Other drug interactions include azole antifungals, conivaptan, clarithromycin, protease inhibitors, erythromycin, ciprofloxacin, diltiazem, dronedarone, verapamil, amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor, rifampin, carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, everolimus, and sirolimus. These drugs should not be taken concurrently with venetoclax. If warfarin is used concurrently with venetoclax, then it is recommended to increase the frequency of international normalized ratio (INR) monitoring for increased bleeding or other toxicity due to the warfarin. If venetoclax must be taken concurrently with digoxin, then the digoxin should be taken at least six hours before the venetoclax.

The amount of venetoclax that is prescribed depends on many factors, including your general health, other health problems, your absolute neutrophil count (ANC), or other drugs you are taking. Your doctor will determine your dose and schedule.

Venetoclax Side Effects:
The side effects of venetoclax and their severity depend on how much of the drug is given. High doses may produce more severe side effects. Most people will not experience all the side effects listed. Side effects are often predictable in terms of their onset, duration, and severity. They are almost always reversible and will go away after therapy is stopped. There is no relationship between the presence of side effects and the effectiveness of the medication.

The following side effect is common (occurring in greater than 30% of patients) in patients taking venetoclax: low white blood cell counts which increases the risk of infection, such as pneumonia, blood infection (sepsis), diarrhea, and nausea.

The following are less common side effects (occurring in about 10-29% of patients): anemia, low platelets (increases risk of bleeding), upper respiratory tract infections (cold symptoms), fatigue, high or

low potassium in the blood, fever, vomiting, headaches, high phosphate in the blood, constipation, cough, swelling, back pain, pyrexia (raised body temperature or fever), and pneumonia.

Tumor lysis syndrome (TLS) is a serious, but rare, side effect of venetoclax that usually occurs within 24-48 hours of the initiation of therapy and may occur because of treatment. With treatment, large amounts of cancerous cells are rapidly killed. These cells release uric acid, potassium, and phosphorous into the bloodstream and can lead to kidney failure. Care must be taken to prevent tumor lysis syndrome. **While taking venetoclax, drink at least two to three quarts of fluid every 24 hours, particularly the 48 hours before the first dose, on the day of the first dose, and anytime the dose is increased, unless instructed otherwise by the health care team. It is important that the health care provider knows immediately if you are unable to urinate or have unusual symptoms.**

What Should I Tell My Health Care Provide Before I Take This Medicine?
Before starting venetoclax treatment, make sure your health care provider knows about any other medications being taken. They need to know if you have any of these conditions: gout, high levels of uric acid in the blood, kidney disease, liver disease, low or high levels of potassium, phosphorus, or calcium in the blood, an unusual or allergic reaction to venetoclax, other medicines, foods, dyes, or preservatives. Do not receive any kind of immunization or vaccination while on venetoclax without the doctor's approval. The immune response to vaccines may be diminished by venetoclax. Live attenuated vaccines should not be administered prior to, during, or after treatment until B-cell recovery has occurred due to a risk of enhanced vaccine adverse effects.

For both men and women: Use contraceptives and do not conceive a child (get pregnant) while taking venetoclax, as it may be harmful to the fetus. Barrier methods of contraception, such as condoms, are recommended during treatment and at least one month after treatment. Discuss with your doctor when it is safe to become pregnant or conceive a child after therapy. Do not breastfeed while taking this medication due to potential secretion into breast milk. Venetoclax may cause fertility problems in males. This may affect the ability to father a child. Talk to your health care provider if there are concerns about fertility. Always inform your health care provider if you experience any unusual symptoms.

When to Contact Your Doctor or Health Care Provider:
Contact your doctor or health care provider immediately, day or night, if you should experience any of the following symptoms: fever of 100.5° F (38° C) or higher or chills (both are possible signs of infection).

Contact your health care provider within 24 hours of noticing any of the following symptoms: nausea (interferes with ability to eat and unrelieved with prescribed medications), vomiting, diarrhea (4-6 episodes in a 24 hour period), unable to eat (from causes other than nausea) or drink for 24 hours or have signs of dehydration (tiredness, thirst, dry mouth, dark and decreased amount of urine), dizziness, whites of your eyes turn yellow, signs of infection (cough without mucous, nasal drainage, burning with urination, redness or swelling, pus formation at the site of an injury or incision), fatigue that interferes with activities of daily living (showering, bathing, making meals, etc.), swelling, any signs of unusual bleeding or bruising, black, tarry, or bloody stools, blood in your urine, or heavy menstrual bleeding.

Self-Care Tips While Taking Venetoclax:
There may be an increased risk of infection, so try to avoid crowds or people with colds and report fever or any other signs of infection immediately to your health care provider. Wash your hands often. Do not touch your eyes or the inside of your nose unless you have just washed your hands and have not touched anything else in the meantime.

If nausea becomes a problem, take anti-nausea medications, as prescribed by your health care team, and eat small, frequent meals. Sucking on lozenges and chewing gum may also help.

Contact your medical team before scheduling dental appointments or procedures.

Use an electric razor to minimize bleeding. Avoid contact sports or activities that could cause injury.

Avoid sun exposure. Wear SPF 15 (or higher) sun block and protective clothing. Get plenty of rest and maintain good nutrition. Discuss all symptoms or side effects with your health care team. They can prescribe medications and /or offer other suggestions that are effective in managing such problems.

Monitoring and Testing While Taking Venetoclax:
While taking venetoclax your medical team will monitor side effects and check response to therapy. Periodic blood work will be obtained to monitor the complete blood count (CBC), as well as the function of other organs, such as kidneys and liver.

Acknowledgments
The IWMF acknowledges the important contributions to treatment guidelines discussed here that have been published by the International Workshops on Waldenstrom's Macroglobulinemia (IWWM) and the National Comprehensive Cancer Network (NCCN®). The IWMF acknowledges Dr. Jorge J. Castillo, Dana-Farber Cancer Institute, for his review of this Fact Sheet.

About the IWMF
The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for a cure."
More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

Venetoclax Fact Sheet

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.

Adapted from the Chemocare website www.chemocare.com, sponsored by the Cleveland Clinic, and BC Cancer Drug Manual® www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.