

Understanding BCL-2 Inhibitor Treatment and Management of Potential Side Effects

Understanding the Role of BCL-2 in Hematologic Malignancies

- BCL-2 is a protein that helps control whether a cell lives or dies by a process known as apoptosis¹
- In many B-cell leukemias and lymphomas, such as **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)**, overexpression of BCL-2 leads to abnormal and unregulated cell growth¹
 - This is associated with resistance to cancer treatments and worse outcomes
- Venetoclax (*Venclexta*) is an inhibitor of BCL-2 and currently the only approved therapy in this class of drugs²

Approved Indications for Venetoclax

CLL or SLL

Venetoclax is FDA approved for **CLL** or **SLL**²

- In CLL/SLL, venetoclax may be combined with other treatments such as intravenous CD20 monoclonal antibodies (obinutuzumab, rituximab)³

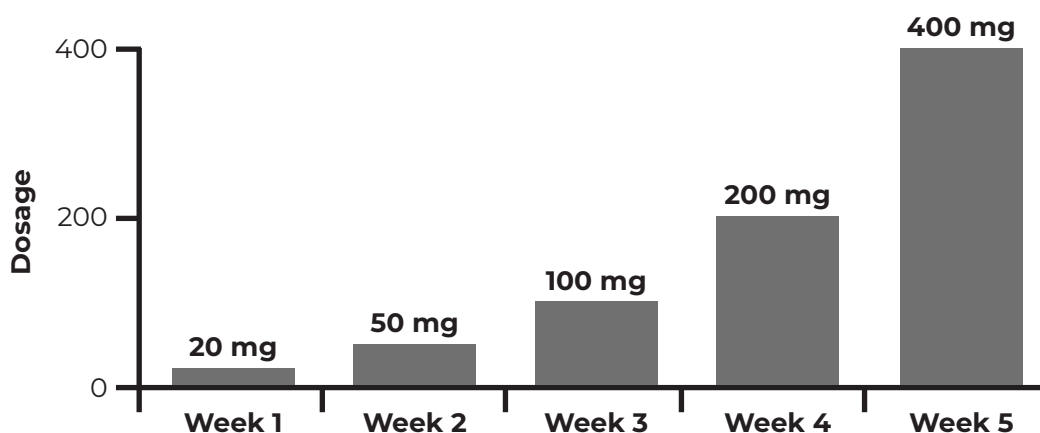
AML

Venetoclax is FDA approved in combination with azacitidine, decitabine, or low-dose cytarabine (LDAC) for newly diagnosed **acute myeloid leukemia (AML)** in those age 75 years or older or who have medical conditions for which they cannot receive standard chemotherapy²

Dosage and Administration Considerations for Venetoclax in CLL/SLL²

- When taken by itself, venetoclax is given at a dose of 400 mg
- The dose of venetoclax may be increased gradually from 20 mg to 400 mg (ramped up) over the first 5 weeks to decrease your risk of tumor lysis syndrome (TLS) (see “Understanding TLS” section).

Venetoclax Weekly Ramp-up Schedule for CLL/SLL



Dosing when venetoclax is given with **obinutuzumab (O)**; 1 cycle = 28 days:

Cycle 1

1	2	3	4	5	6	7
O	O					
8	9	10	11	12	13	14
O						
15	16	17	18	19	20	21
O						
22	23	24	25	26	27	28
V	V	V	V	V	V	V

Venetoclax ramp-up begins on Day 22.

Cycles 2-6

1	2	3	4	5	6	7
OV	V	V	V	V	V	V
8	9	10	11	12	13	14
V	V	V	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V

Note: Venetoclax continues through **cycle 12**.

Dosing when venetoclax is given with **rituximab (R)**; 1 cycle = 28 days:

Venetoclax Ramp-up

1	2	3	4	5	6	7
V	V	V	V	V	V	V
8	9	10	11	12	13	14
V	V	V	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V
29	30	31	32	34	35	36
V	V	V	V	V	V	V

Cycles 1-6

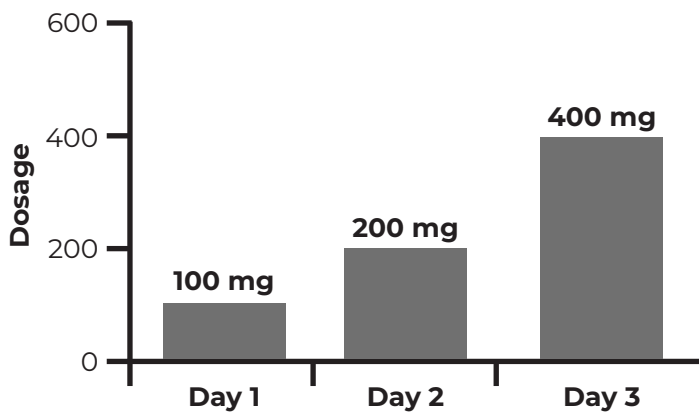
1	2	3	4	5	6	7
RV	V	V	V	V	V	V
8	9	10	11	12	13	14
V	V	V	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V

Note: Rituximab is a higher dose with cycle 1. Venetoclax continues through **Month 24**.

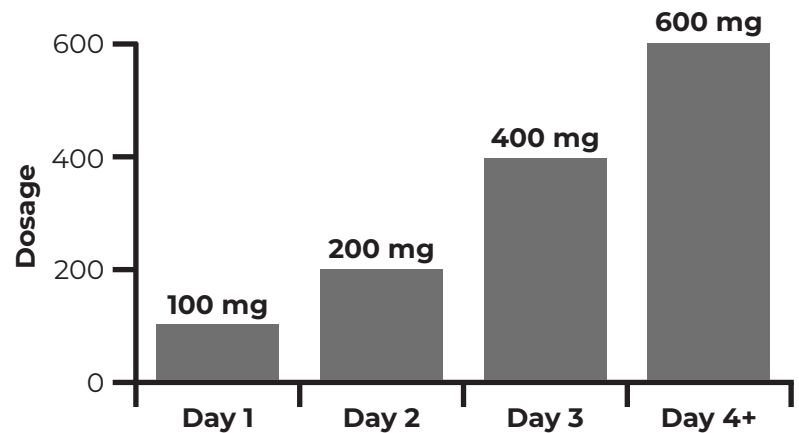
Dosage and Administration Considerations for Venetoclax in AML^{2,4,5}

- When given for AML, venetoclax is taken in combination with other medications that are administered intravenously or subcutaneously
- To decrease your risk of TLS, the dose is increased from 100 mg to 400 mg or 600 mg (ramped up) over the first 3-4 days
- Your doctor may adjust your ramp-up and maximum venetoclax dosage based on the other medications you take

Venetoclax Daily Ramp-up Schedule for AML + Azacitidine or Decitabine



Venetoclax Daily Ramp-up Schedule for AML + LDAC



Dosing Schedule in AML: 28-Day Cycles

Venetoclax + Azacitidine (A)*

1	2	3	4	5	6	7
AV	AV	AV	AV	AV	AV	AV
8	9	10	11	12	13	14
V	V	V	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V

Venetoclax + Decitabine (D)

1	2	3	4	5	6	7
DV	DV	DV	DV	DV	V	V
8	9	10	11	12	13	14
V	V	V	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V

Venetoclax + LDAC (C)

1	2	3	4	5	6	7
CV	CV	CV	CV	CV	CV	CV
8	9	10	11	12	13	14
CV	CV	CV	V	V	V	V
15	16	17	18	19	20	21
V	V	V	V	V	V	V
22	23	24	25	26	27	28
V	V	V	V	V	V	V

*Azacitidine may be given in a 5-2-2 series with dosing during 5 weekdays, 2 weekend days off, and then dosing for 2 more days.

These combinations, with venetoclax taken daily, will be continued until the therapy is no longer working or you experience significant side effects. Your doctor will discuss with you when to stop these medications.⁴

How Should You Take Venetoclax?

How to Take

- Take venetoclax once daily (at about the same time each day) with a meal and water
- Swallow venetoclax whole; do not chew, crush, or break the tablets
- Keep venetoclax in the original container, and store at room temperature
- Tell your doctor about all the medicines you take, including over-the-counter medications, vitamins, and herbal supplements

What to Avoid

- Do not drink grapefruit juice or eat grapefruit, Seville oranges, or starfruit
- Do not receive live-attenuated vaccines before, during, or after treatment with venetoclax until your physician tells you it is okay

Management of Select Side Effects With Venetoclax^{2,3,4,7,8}

Diarrhea

- Stay hydrated
- Avoid foods high in fiber
- **Call your doctor** if you have more than 7 stools per day or are dehydrated

Nausea

- Make sure your doctor gives you an anti-nausea medication to take at home if needed
- Eat small amounts frequently and stay hydrated
- **Call your doctor** if the anti-nausea medication does not help your nausea or stop you from vomiting, or if you cannot stay adequately hydrated

Neutropenia*

- Keep up with your scheduled lab work
- Antibacterial and/or antifungal medications may be started during periods of neutropenia
- **Go to the emergency room** if you have a fever or any signs or symptoms of infection

TLS

- Drink plenty of water (6-8 glasses each day) during treatment, starting 2 days before your first dose of venetoclax
- Keep up with your scheduled lab work
- Take any medications prescribed by your doctor, such as allopurinol
- **Call your doctor or seek immediate medical attention** if you have fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, or muscle or joint pain

*Neutropenia is a low level of neutrophils, which are a type of white blood cell.

Venetoclax may need to be stopped and/or the dose reduced to manage side effects

Understanding TLS²⁻⁶

- TLS is a possible severe side effect that occurs when tumor cells break open as they die quickly, releasing their contents into the bloodstream
 - This causes changes in electrolytes, which can harm your organs
 - TLS is a serious condition that can result in the need for dialysis and in rare cases may even cause death if not treated
 - TLS can occur shortly after starting venetoclax and when increasing the dosage
- The risk of TLS is greater with CLL and SLL than with AML
- Your doctor will determine your risk for TLS prior to starting venetoclax
- Signs of TLS
 - Any of the following: nausea, vomiting, shortness of breath, irregular heartbeat, cloudy urine, lethargy, or joint discomfort^{3,4}
- Management of TLS
 - Staying hydrated is key!
 - Depending on your risk level, your doctor may prescribe a tablet called allopurinol or an injection called rasburicase to help manage the buildup of uric acid or harmful pieces from the tumor cells in the bloodstream
 - You may need more frequent lab work at the start of taking venetoclax and during dose increases to monitor your electrolytes and kidney function
 - In some cases, you may need to start venetoclax in the hospital

Questions to Ask Your Doctor

1. Will I receive venetoclax alone or with another drug?

2. Will I need to be in the hospital to start venetoclax?

3. What should I look for with respect to side effects?

4. When should I call my care team about concerns?

References

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