



For Healthcare Professionals

STARTING PATIENTS WITH CLL/SLL ON VENCLEXTA

1L=first-line; R/R=relapsed/refractory; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

Indication

- VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Select Important Safety Information

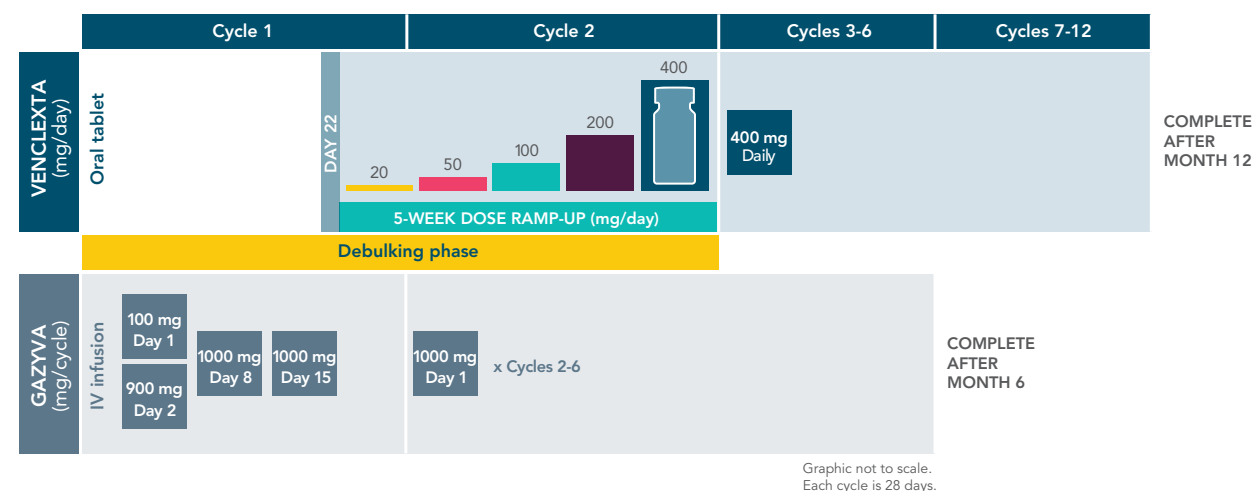
- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).
- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA. Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.
- Grade 3 or 4 neutropenia occurred in patients treated with VENCLEXTA. Monitor blood counts and for signs of infection; manage as medically appropriate.
- Fatal and serious infections such as pneumonia and sepsis have occurred in patients with VENCLEXTA. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.
- Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs.
- VENCLEXTA may cause embryo-fetal harm. Advise females of reproductive potential to avoid pregnancy during treatment.

Please see additional Important Safety Information on pages 20 and 21.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

 **VENCLEXTA**[®]
venetoclax tablets 10mg, 50mg, 100mg

The only chemo-free regimen designed to stop treatment at 12 months in 1L CLL...¹

VENCLEXTA + GAZYVA® (obinutuzumab) (VEN+G) for 1L CLL/SLL



- The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up to help reduce tumor burden (debulk) and decrease the risk of TLS
- After the first treatment cycle of GAZYVA and before the VENCLEXTA dose ramp-up, patients' ALC was reduced by 98% (from a median count of 55×10^9 cells/L at baseline to a median count of 1.27×10^9 cells/L at Day 15)^{2*}
- Per the trial protocol, tumor burden was assessed based on ALC and lymph node size. The effect of the first GAZYVA treatment cycle on lymph node size was not evaluated
- Tumor burden assessments, including radiographic evaluation and blood chemistry assessment, are recommended prior to VENCLEXTA initiation to assess the risk for TLS

*Median lymphocyte counts are descriptive in nature and not powered for any type of comparison. Changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators.

IV=intravenous; TLS=tumor lysis syndrome; ALC=absolute lymphocyte count.

GAZYVA

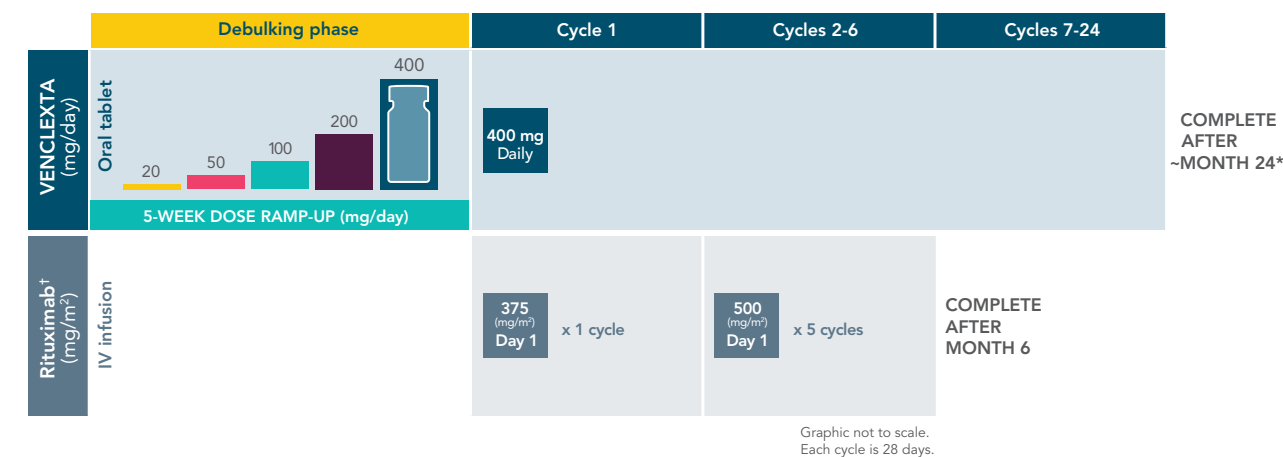
- On Cycle 1, Days 1 and 2 administer GAZYVA 100 mg and 900 mg, respectively
- Administer GAZYVA 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles
- See pages 4-6 for an overview of GAZYVA dosing and administration

VENCLEXTA

- On Cycle 1, Day 22 start VENCLEXTA according to the 5-week ramp-up schedule
- The VENCLEXTA starting dose is 20 mg once daily for 7 days, ramping up weekly to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily
- After completing the ramp-up schedule on Cycle 2, Day 28, patients should continue VENCLEXTA 400 mg once daily from Cycle 3, Day 1 until the last day of Cycle 12

...and ~24 months* in R/R CLL¹

VENCLEXTA + rituximab (VEN+R) for R/R CLL/SLL



- To gradually reduce tumor burden (debulk) and decrease the risk of TLS, start with the 5-week VENCLEXTA dose ramp-up

*24 months from Cycle 1, Day 1 of rituximab.

[†]Start rituximab after patient has received the 400 mg dose of VENCLEXTA for 7 days.

VENCLEXTA

- The VENCLEXTA starting dose is 20 mg once daily for 7 days, ramping up weekly to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily
- After ramp-up, VENCLEXTA should be taken at the recommended daily dose for 24 months

Rituximab

- Start rituximab 375 mg/m² after the patient has received the 400 mg dose of VENCLEXTA for 7 days
- Administer rituximab 500 mg/m² on Day 1 of each subsequent cycle, for a total of 6 cycles

Note: VENCLEXTA may also be given as monotherapy until disease progression or unacceptable toxicity. Please see the full Prescribing Information for more information.

Select Important Safety Information

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- In patients with CLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.

GAZYVA® (obinutuzumab) dosing and administration overview³

6-cycle dosing schedule

Each dose of GAZYVA is 1000 mg administered intravenously with the exception of the first infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg).

GAZYVA dosing schedule			
Day of treatment cycle		Dose	Rate of infusion
Cycle 1 (loading doses)	Day 1	100 mg	Rate of infusion: <ul style="list-style-type: none">Administer at 25 mg/hr over 4 hoursDo not increase the infusion rate
	Day 2	900 mg	Rate of infusion: <ul style="list-style-type: none">Administer at 50 mg/hrThe rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 8	1000 mg	Rate of infusion: <ul style="list-style-type: none">If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hrIf an infusion reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	

IRRs=infusion-related reactions.

Premedication and administration

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of TLS
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur

Select Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Please see additional Important Safety Information for GAZYVA on page 7.

Please see accompanying full Prescribing Information for GAZYVA or visit

https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

Recommended premedications

The following premedications are recommended before GAZYVA infusion begins to reduce the risk of IRRs:

	Cycle 1, Days 1 and 2	All subsequent infusions		
Complete before infusion	All patients	All patients	Patients with an IRR (grade 1-2) with the previous infusion	Patients with a grade 3 IRR with the previous infusion OR with a lymphocyte count >25 x 10 ⁹ /L prior to next treatment
60 minutes prior Intravenous glucocorticoid*†	✓			✓
30 minutes prior Antihistamine‡	✓		✓	✓
30 minutes prior Acetaminophen§	✓	✓	✓	✓

*20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.

†If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

‡Eg, 50 mg diphenhydramine.

§650-1000 mg.

Premedication and close monitoring are recommended for all patients

- Patients with preexisting cardiac or pulmonary conditions are at a greater risk of experiencing more severe infusion reactions
- Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration
- Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10⁹/L), or renal impairment are considered at risk of TLS and should receive prophylaxis. Premedicate with antihyperuricemics (eg, allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed
- Patients with grade 3 to 4 neutropenia lasting more than 1 week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to grade 1 or 2. Antiviral and antifungal prophylaxis should be considered

GAZYVA® (obinutuzumab) dosing and administration overview (cont'd)³

Adjusting infusions in case of IRRs

If a patient experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:

Infusion reactions	Recommendations per prescribing information
Grade 4 (life threatening)	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	Interrupt infusion and manage symptoms <ul style="list-style-type: none">Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dosePermanently discontinue treatment if patients experience a grade 3 infusion-related symptom at rechallenge<ul style="list-style-type: none">The Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further
Grades 1-2 (mild to moderate)	Reduce infusion rate or interrupt infusion and treat symptoms <ul style="list-style-type: none">Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose<ul style="list-style-type: none">The Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further

- Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed

Incidence of infusion reactions⁴

- In the VEN+G clinical trial, infusion-related reactions (any grade) occurred in 48% (205/426) of patients. Grade 3 or 4 infusion-related reactions occurred in 9% (40/426) of patients

Please see additional Important Safety Information for GAZYVA on page 7.
Please see accompanying full Prescribing Information for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

Important Safety Information for GAZYVA

Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA

Contraindications

- GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g. anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Additional Warnings and Precautions

- Infusion Reactions:** Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions
- Hypersensitivity Reactions Including Serum Sickness:** Discontinue GAZYVA permanently
- Tumor Lysis Syndrome (TLS):** Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance
- Infections:** Monitor for infection during and after treatment
- Neutropenia:** Monitor for infection and promptly treat
- Thrombocytopenia:** Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support
- Immunization:** Do not administer live virus vaccines prior to or during GAZYVA treatment

Additional Important Safety Information

- The most common adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were infusion reactions (66%), neutropenia (38%), thrombocytopenia (14%), anemia (11%), pyrexia (9%), cough (7%), nausea (12%), and diarrhea (10%)








You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2555. You may contact the FDA by visiting www.fda.gov/medwatch, or calling 1-800-FDA-1088.

Please see accompanying full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.

Initiating the 5-week VENCLEXTA dose ramp-up¹

3 STEPS: ASSESS, PREPARE, INITIATE

The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

STEP 1: ASSESS PRIOR TO VENCLEXTA	STEP 2: PREPARE 2-3 DAYS PRIOR TO FIRST DOSE	STEP 3: INITIATE FIRST 5 WEEKS OF TREATMENT
Tumor burden assessment	Anti- hyperuricemics*	Hydration [†] Blood chemistry monitoring ^{‡§}
LOW TUMOR BURDEN All LN <5 cm AND ALC <25 x 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L)  Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6-8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
MEDIUM TUMOR BURDEN Any LN 5 cm to <10 cm OR ALC ≥25 x 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L)  Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6-8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CLcr <80 mL/min; see below for monitoring in hospital
HIGH TUMOR BURDEN Any LN ≥10 cm OR Any LN ≥5 cm AND ALC ≥25 x 10 ⁹ /L	 Allopurinol Consider rasburicase if baseline uric acid is elevated	Oral (1.5-2 L)  and  IV (150-200 mL/hr as tolerated) In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6-8 hours, 24 hours

- Step 1:** Assess tumor burden, renal function, and comorbidities (CLcr <80 mL/min), and assess and correct baseline blood chemistries^{||}
- Step 2:** Begin administering anti-hyperuricemics 2-3 days prior and initiate oral and/or IV hydration 2 days prior[†]
- Step 3:** Initiate 5-week dose ramp-up^{||} and monitor blood chemistry (review in real time). For 1L treatment, initiate the ramp-up on Cycle 1, Day 22^{||}

The risk of TLS may decrease as tumor burden decreases

*Start allopurinol or xanthine oxidase inhibitor 2-3 days prior to initiation of VENCLEXTA.

[†]1.5-2 L of water (6-8 glasses) should be consumed every day starting 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

[‡]Review in real time.

[§]For patients at risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours at each subsequent ramp-up dose.

^{||}Potassium, uric acid, phosphorus, calcium, and creatinine; correct any pre-existing abnormalities.

^{||}Starting at 20 mg and escalating weekly to 50 mg, 100 mg, 200 mg, and then 400 mg once daily.

LN=lymph node; CLcr=creatinine clearance.

Ramp-up, monitoring, and prophylaxis reduced clinical TLS¹

MANAGEMENT OF TLS

By implementing the TLS prophylaxis and monitoring protocol, 0% incidence of clinical TLS was observed with VENCLEXTA in 2 CLL trials^{1,5}

In both the VEN+G and VEN+R trials, no clinical TLS was observed in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures.

- VEN+G trial**
- Incidence of laboratory TLS occurred in 1% (3/212) of patients treated with VEN+G. All 3 TLS events resolved and did not lead to withdrawal from the study
 - GAZYVA[®] (obinutuzumab) administration was delayed in 2 cases in response to the TLS events
- VEN+R trial**
- Incidence of laboratory TLS occurred in 3% (6/194) of patients treated with VEN+R. All TLS events occurred during the ramp-up period and were resolved within 2 days. All 6 patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA

To assess the risk of TLS, tumor burden assessments, including radiographic evaluation and blood chemistry, are recommended prior to initiation of VENCLEXTA

- Considerations for TLS with VENCLEXTA**
- The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CLcr <80 mL/min) further increases the risk
 - Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase, and may require VENCLEXTA dose adjustment (see pages 10 and 11 for dose modification information)
 - Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose and each dose increase
- CYP3A=Cytochrome P450 3A; P-gp=P-glycoprotein.

Select Important Safety Information

- Tumor Lysis Syndrome**
- VENCLEXTA poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.
 - Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
 - Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.
- Hepatic Impairment**
- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Dose modifications¹

Interrupt dosing or reduce dose for toxicities

- For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess the risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the ramp-up schedule)

Recommended VENCLEXTA dose modifications for toxicities*	
TLS	
Any occurrence: Blood chemistry changes or symptoms suggestive of TLS	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
	For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose. See dose reduction guidelines on page 11.
	For any events of clinical TLS, [†] resume at a reduced dose following resolution. See dose reduction guidelines on page 11.
Nonhematologic toxicities	
1st occurrence: Grade 3 or 4 nonhematologic toxicities	Interrupt VENCLEXTA. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required.
2nd and subsequent occurrences: Grade 3 or 4 nonhematologic toxicities	Interrupt VENCLEXTA. Follow dose reduction guidelines on page 11 when resuming VENCLEXTA treatment after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic toxicities	
1st occurrence: Grade 3 neutropenia with infection or fever or grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
2nd and subsequent occurrences: Grade 3 neutropenia with infection or fever or grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose-reduction guidelines on page 11 when resuming VENCLEXTA treatment after resolution. A larger dose reduction may occur at the discretion of the physician.

Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks

*Adverse reactions were graded using NCI CTCAE version 4.0.
[†]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.
NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.

Dose reduction for toxicity during VENCLEXTA treatment	
Dose at interruption, mg	Restart dose, mg*
400	300
300	200
200	100
100	50
50	20
20	10

*During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

Dosage modifications for concomitant use with strong or moderate CYP3A inhibitors or P-gp inhibitors

Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of TLS.

Management of potential VENCLEXTA interactions with CYP3A and P-gp inhibitors		
Coadministered drug	Initiation and ramp-up phase	Steady daily dose [†] (after ramp-up phase)
Posaconazole	Contraindicated	Reduce VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitor	Reduce VENCLEXTA dose by at least 50%	
P-gp inhibitor		

[†]Consider alternative medications or reduce the VENCLEXTA dose as described in this table.

- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure
- Resume the VENCLEXTA dose that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor

Dosage modifications for patients with severe hepatic impairment

- Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity

Instructions for taking VENCLEXTA¹

Advise patients:



To take VENCLEXTA exactly as prescribed and **not to change their dose or to stop taking VENCLEXTA** unless they are told to do so by their doctor.



To take VENCLEXTA **once daily with a meal and water** at approximately the same time each day.



That VENCLEXTA tablets should be swallowed whole and **not chewed, crushed, or broken.**



To **keep VENCLEXTA in the original packaging during the first 4 weeks of treatment**, and not to transfer the tablets to a different container.



Of the importance of **keeping scheduled appointments** for blood work or other laboratory tests.



To be adequately hydrated every day when taking VENCLEXTA to reduce the risk of TLS. The recommended volume is **6-8 glasses (~56 ounces) of water** every day starting 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase.



To **avoid grapefruit products, Seville oranges, and starfruit** during treatment with VENCLEXTA.

If a patient misses a dose within 8 hours of the time it is usually taken:

The patient should take the missed dose right away and take the next dose as usual.

If a patient misses a dose by more than 8 hours:

The patient should not take the missed dose and should take the next dose at the usual time.

If a patient vomits following dosing:

No additional dose should be taken that day. The next dose should be taken at the usual time the following day.

Select Important Safety Information

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies.
- Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Summary of VEN+G safety data¹

The safety of VEN+G versus GClb was evaluated in an open-label, randomized, phase 3 study in patients with previously untreated CLL

- In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and within 28 days of the last VENCLEXTA treatment were reported in 2% (4/212) of patients. Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each)
- The median duration of exposure to VENCLEXTA was 10.5 months (range: 0 to 13.5 months). The median number of cycles was 6 for obinutuzumab and 12 for chlorambucil
- Adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 21%, and dose interruption in 74%
- Neutropenia led to dose interruption of VENCLEXTA in 41% of patients, reduction in 13%, and discontinuation in 2%

Common (≥10%) adverse reactions in patients treated with VEN+G				
Adverse Reaction by Body System	VEN+G		GClb	
	Any Grade (%) n=212	Grade ≥3 (%) n=212	Any Grade (%) n=214	Grade ≥3 (%) n=214
Blood and lymphatic system disorders				
Neutropenia*	60	56	62	52
Anemia*	17	8	20	7
Gastrointestinal disorders				
Diarrhea	28	4	15	1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				
Fatigue*	21	2	23	1
Infections and infestations				
Upper respiratory tract infection*	17	1	17	1

*Includes multiple adverse reaction terms.
GClb=GAZYVA + chlorambucil.

For common laboratory abnormalities data, please see Table 10 in the VENCLEXTA full Prescribing Information.

During treatment with single-agent VENCLEXTA after completion of VEN+G combination treatment:

- The most common (all grades) adverse reaction (≥10% patients) reported was neutropenia (26%)
- The most common grade ≥3 adverse reactions (≥2% patients) were neutropenia (23%) and anemia (2%)

Summary of VEN+R safety data¹

The safety of VEN+R versus BR was evaluated in the open-label, randomized, phase 3 MURANO study in patients with CLL who had received at least one prior therapy

- In the VEN+R arm, fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of rituximab were reported in 2% (4/194) of patients. Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with the most frequent (≥5%) being pneumonia (9%)
- At the time of data analysis, the median duration of exposure was 22 months in the VEN+R arm compared with 6 months in the BR arm
- Discontinuation due to any adverse events occurred in 16% of patients on VEN+R compared with 10% of patients on BR
- Dose reductions due to adverse events occurred in 15% of patients in both arms
- Dose interruptions due to adverse events occurred in 71% of patients on VEN+R compared with 40% of patients on BR
- In the VEN+R arm, neutropenia led to dose interruption of VENCLEXTA in 46% of patients and discontinuation in 3%, and thrombocytopenia led to discontinuation in 3% of patients
- The MURANO trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for VEN+R compared with BR, for any specific adverse reaction or laboratory abnormality

Common (≥10%) adverse reactions reported with ≥5% higher all-grade or ≥2% higher grade ≥3 incidence in patients treated with VEN+R compared with BR				
Adverse Reaction by Body System	VEN+R		BR	
	Any Grade (%) n=194	Grade ≥3 (%) n=194	Any Grade (%) n=188	Grade ≥3 (%) n=188
Blood and lymphatic system disorders				
Neutropenia*	65	62	50	44
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Infections and infestations				
Upper respiratory tract infection*	39	2	23	2
Lower respiratory tract infection*	18	2	10	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	19	1	13	0
Metabolism and nutrition disorders				
Tumor lysis syndrome	3	3	1	1

*Includes multiple adverse reaction terms.
BR=bendamustine + rituximab.

For common laboratory abnormalities data, please see Table 12 in the VENCLEXTA full Prescribing Information.

Other adverse reactions (all grades) reported in ≥10% of patients in the VEN+R arm in MURANO, and other important adverse reactions:

- Fatigue (22%), cough (22%), nausea (21%), anemia (16%), pyrexia (15%), thrombocytopenia (15%), constipation (14%), abdominal pain (13%), rash (13%), headache (11%), insomnia (11%), mucositis (10%), pneumonia (10%), vomiting (8%), febrile neutropenia (4%), sepsis (1%)

During treatment with single agent VENCLEXTA after completion of VEN+R combination treatment:

- The most common (all grades) adverse reactions (≥10% patients) reported were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infection (11%)
- The most common grade 3 or 4 adverse reactions (≥2% patients) were neutropenia (12%) and anemia (3%)

LOW OR MEDIUM TUMOR BURDEN¹

LOW TUMOR BURDEN: All LN <5 cm AND ALC <25 x 10⁹/L
MEDIUM TUMOR BURDEN: Any LN 5 cm to <10 cm OR ALC ≥25 x 10⁹/L

This example is provided to help you in using the full Prescribing Information and is for illustrative purposes only. No patient is the same. Refer to the full Prescribing Information when making treatment decisions.

Order VENCLEXTA Starting Pack: Dosing for Weeks 1-4 ✓
Order bottle of 100 mg tablets: Dosing for Week 5+ ✓

STEP 1: ASSESS (Prior to Treatment)

Assess tumor burden, renal function and comorbidities, and baseline blood chemistries (see page 8) ✓

STEP 2: PREPARE (2-3 Days Before Treatment)

- **Anti-hyperuricemics:** Start allopurinol or xanthine oxidase inhibitor 2 to 3 days before initiation ✓
- 💧 **Hydration:** Ensure oral hydration with 1.5-2 L daily, starting 2 days before initiation, on the day of the first dose and at each ramp-up dose. For medium tumor burden patients, consider administering additional IV hydration. Administer IV hydration for any patient who cannot tolerate oral hydration ✓

STEP 3: INITIATE (5-Week Dose Ramp-up and Monitoring)

5-Week Dose Ramp-Up (Oral, Once Daily): Patient takes VENCLEXTA tablet(s) by mouth daily with food and water at approximately the same time each day as prescribed ✓

🧪 **Blood Chemistry Monitoring: Potassium, calcium, creatinine, phosphorus, uric acid** (review in real time)
Evaluate and manage any abnormalities promptly.

		EXAMPLE TIMING	ACTUAL TIMING	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
Before dose	🧪 Pre-dose labs drawn			✓	✓	✓	✓	✓
	VENCLEXTA ramp-up dose initiated <small>This dose and subsequent can be taken at home, if instructed</small>	8 AM		✓	✓	✓	✓	✓
DAY 1	🧪 6-8 hours: Post-dose labs drawn*	2-4 PM		✓	✓			
	Lab results evaluated			✓	✓			
DAY 2	🧪 24 hours: Post-dose labs drawn*	8 AM		✓	✓			
	Lab results evaluated <small>Patient instructed to take Day 2 dose</small>			✓	✓			

*For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose (Weeks 3-5).

✓ Continue VENCLEXTA 400 mg once daily for the prescribed duration.

- For additional information about TLS prophylaxis and monitoring, please see page 8 in this brochure and the full Prescribing Information
- For information regarding dose modifications based on toxicities, drug interactions, and severe hepatic impairment, please see pages 10 and 11 in this brochure and the full Prescribing Information

Please see additional Important Safety Information on pages 20 and 21.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

HIGH TUMOR BURDEN¹

HIGH TUMOR BURDEN: Any LN ≥10 cm, OR Any LN ≥5 cm AND ALC ≥25 x 10⁹/L

This example is provided to help you in using the full Prescribing Information and is for illustrative purposes only. No patient is the same. Refer to the full Prescribing Information when making treatment decisions.

Order VENCLEXTA Starting Pack: Dosing for Weeks 1-4 ✓
Order bottle of 100 mg tablets: Dosing for Week 5+ ✓

STEP 1: ASSESS (Prior to Treatment)

Assess tumor burden, renal function and comorbidities, and baseline blood chemistries (see page 8) ✓

STEP 2: PREPARE (2-3 Days Before Treatment)

- **Anti-hyperuricemics:** Start allopurinol or xanthine oxidase inhibitor 2 to 3 days before initiation. Consider rasburicase if baseline uric acid is elevated ✓
- 💧 **Hydration:** Ensure adequate oral hydration with 1.5-2 L daily, starting 2 days before initiation, on the day of the first dose and at each ramp-up dose, and IV 150-200 mL/hr as tolerated. Administer IV hydration for any patient who cannot tolerate oral hydration ✓

STEP 3: INITIATE (5-Week Dose Ramp-up and Monitoring)

5-Week Dose Ramp-Up (Oral, Once Daily): Patient takes VENCLEXTA tablet(s) by mouth daily with food and water at approximately the same time each day as prescribed ✓

🧪 **Blood Chemistry Monitoring: Potassium, calcium, creatinine, phosphorus, uric acid** (review in real time)
Evaluate and manage any abnormalities promptly.

		EXAMPLE TIMING	ACTUAL TIMING	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
Before dose	🧪 Pre-dose labs drawn			✓	✓	✓	✓	✓
	VENCLEXTA ramp-up dose initiated	8 AM		✓	✓	✓	✓	✓
DAY 1	🧪 4 hours: Post-dose labs drawn	12 PM		✓	✓			
	🧪 8 hours: Post-dose labs drawn <small>(Weeks 3-5: 6-8 hours acceptable)</small>	4 PM		✓	✓			
	🧪 12 hours: Post-dose labs drawn	8 PM		✓	✓			
DAY 2	🧪 24 hours: Post-dose labs drawn	8 AM		✓	✓			
	Lab results evaluated <small>Patient instructed to take Day 2 dose</small>			✓	✓			

✓ Continue VENCLEXTA 400 mg once daily for the prescribed duration.

- For additional information about TLS prophylaxis and monitoring, please see page 8 in this brochure and the full Prescribing Information
- For information regarding dose modifications based on toxicities, drug interactions, and severe hepatic impairment, please see pages 10 and 11 in this brochure and the full Prescribing Information

LOW OR MEDIUM TUMOR BURDEN¹

This example is provided to help you in using the full Prescribing Information and is for illustrative purposes only. No patient is the same. Refer to the full Prescribing Information when making treatment decisions.

Order VENCLEXTA Starting Pack: Dosing for Weeks 1-4 ✓
Order bottle of 100 mg tablets: Dosing for Week 5+ ✓

STEP 3: INITIATE

WEEK 1

20 mg

Take two 10 mg tablets once daily

DAY 1

6-8 HOUR POST-DOSE LABS

DAY 2

24-HOUR POST-DOSE LABS

DAY 3

DAY 4

DAY 5

DAY 6

DAY 7

PRE-DOSE LABS BEFORE NEXT DOSE

WEEK 2

50 mg

Take one 50 mg tablet once daily

DAY 1

6-8 HOUR POST-DOSE LABS

DAY 2

24-HOUR POST-DOSE LABS

DAY 3

DAY 4

DAY 5

DAY 6

DAY 7

PRE-DOSE LABS BEFORE NEXT DOSE

WEEK 3

100 mg

Take one 100 mg tablet once daily

DAY 1

DAY 2

DAY 3

DAY 4

DAY 5

DAY 6

DAY 7

PRE-DOSE LABS BEFORE NEXT DOSE

WEEK 4

200 mg

Take two 100 mg tablets once daily

DAY 1

DAY 2

DAY 3

DAY 4

DAY 5

DAY 6

DAY 7

PRE-DOSE LABS BEFORE NEXT DOSE

WEEK 5

400 mg

Take four 100 mg tablets once daily

DAY 1

DAY 2

DAY 3

DAY 4

DAY 5

DAY 6

DAY 7

✓ Continue VENCLEXTA 400 mg once daily for the prescribed duration.

STEP 1: ASSESS

Assess tumor burden, renal function and comorbidities, and blood chemistries

STEP 2: PREPARE

2-3 DAYS PRIOR TO VENCLEXTA INITIATION

Start anti-hyperuricemics

2 DAYS PRIOR TO VENCLEXTA INITIATION

Start oral/IV hydration

BEFORE EACH DOSE INCREASE

Pre-dose labs

- Select Instructions for Taking VENCLEXTA
- 1.5-2 L of water (6-8 glasses) should be consumed every day starting 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase
 - Patients should take VENCLEXTA with a meal and water at approximately the same time each day
 - For more information about Instructions for Taking VENCLEXTA, please see page 12 and the full Prescribing Information

- Select Provider Considerations
- For patients with medium tumor burden and CLcr <80 mL/min, consider hospitalization for first doses of 20 mg and 50 mg
 - For medium tumor burden patients, consider administering additional IV hydration
 - Administer IV hydration for any patient who cannot tolerate oral hydration
 - For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose (Weeks 3-5)
 - For information about TLS and prophylaxis, including high tumor burden patients in the in-hospital setting, please see pages 8 and 9 in this brochure and the full Prescribing Information
 - For information regarding dose modifications based on toxicities, drug interactions, and severe hepatic impairment, please see pages 10 and 11 in this brochure and the full Prescribing Information

Blood Chemistry Monitoring: Potassium, calcium, creatinine, phosphorus, uric acid (review in real time)

Evaluate and manage any abnormalities promptly.

IV=intravenous; CLcr=creatinine clearance; TLS=tumor lysis syndrome.
Please see additional Important Safety Information on pages 20 and 21. Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

Important Safety Information for VENCLEXTA

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- In patients with CLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.
- VENCLEXTA poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.
- Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies.
- Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid pregnancy during treatment.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to

Bortezomib and Dexamethasone

- In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- **In patients with CLL receiving combination therapy with obinutuzumab**, serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%).
- **In patients with CLL receiving combination therapy with rituximab**, the most frequent serious adverse reaction ($\geq 5\%$) was pneumonia (9%). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), cough (22%), and nausea (21%).
- **In patients with CLL/SLL receiving monotherapy**, the most frequent serious adverse reactions ($\geq 5\%$) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions ($\geq 20\%$) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%).

Drug Interactions

- Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Adjust VENCLEXTA dosage and closely monitor patients for signs of VENCLEXTA toxicities. Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.
- Monitor international normalized ratio (INR) closely in patients receiving warfarin.

Lactation

- Advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.
- Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

IMPORTANT INFORMATION



Dedicated VENCLEXTA support from oncology nurses
(844) 9-COMPASS/(844) 926-6727 | www.VENCLEXTA.com



Your resource for reliable, effective access and reimbursement support
(888) 249-4918 | www.Genentech-Access.com/VENCLEXTA

BioOncology® Co-pay Card

Helping eligible patients with out-of-pocket costs
for VENCLEXTA, GAZYVA, or RITUXAN
(855) MY-COPAY/(855) 692-6729 CopolyAssistanceNow.com/VENCLEXTA

Contact your AbbVie or Genentech representative

to learn more about VENCLEXTA
or ask questions about treatment initiation

placeholder for clear business card sleeve

Please see Important Safety Information on pages 20 and 21.
Please see accompanying full Prescribing Information
or visit www.rxabbvie.com/pdf/venclexta.pdf.

References: 1. VENCLEXTA Prescribing Information. 2. Data on file, AbbVie Inc. ABVRRTI68219. 3. GAZYVA Prescribing Information, November 2017. 4. Data on file, AbbVie Inc. ABVRRTI68279. 5. Data on file, AbbVie Inc. ABVRRTI68272.

VENCLEXTA® and VENCOMPASS® are registered trademarks of AbbVie Inc.
GAZYVA®, Access Solutions® logo, and BioOncology® are registered trademarks of Genentech, Inc.
RITUXAN® is a registered trademark of Biogen.

abbvie

Genentech
A Member of the Roche Group

 **VENCLEXTA**®
venetoclax tablets 10mg, 50mg, 100mg