A GUIDE FOR HEALTHCARE PROFESSIONALS

INITIATING VENCLEXTA FOR PATIENTS WITH CLL/SLL[1]

- CLL14 was a randomized (1:1), multicenter, open-label, actively controlled phase 3 trial that evaluated the efficacy and safety of VENCLEXTA and GAZYVA® (obinutuzumab) versus GClb for previously untreated CLL in 432 patients with coexisting medical conditions (total CIRS score >6 or creatinine clearance <70 mL/min). The primary endpoint was IRC-assessed PFS[1,2]
- MURANO was a randomized (1:1), multicenter, open-label, actively controlled phase 3 trial that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab versus bendamustine in combination with rituximab in 389 patients with CLL who had received at least one line of prior therapy. The primary endpoint was IRC-assessed PFS[1,3]

1L=first line; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma; GClb=GAZYVA + chlorambucil; CIRS=Cumulative Illness Rating Scale; IRC=independent review committee; PFS=progression-free survival.

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 treated with VENCLEXTA. The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.
- Grade 3 or 4 neutropenia occurred in patients treated with VENCLEXTA. Monitor complete 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 for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution.
- 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 use effective contraception during treatment and for 30 days after the last dose.

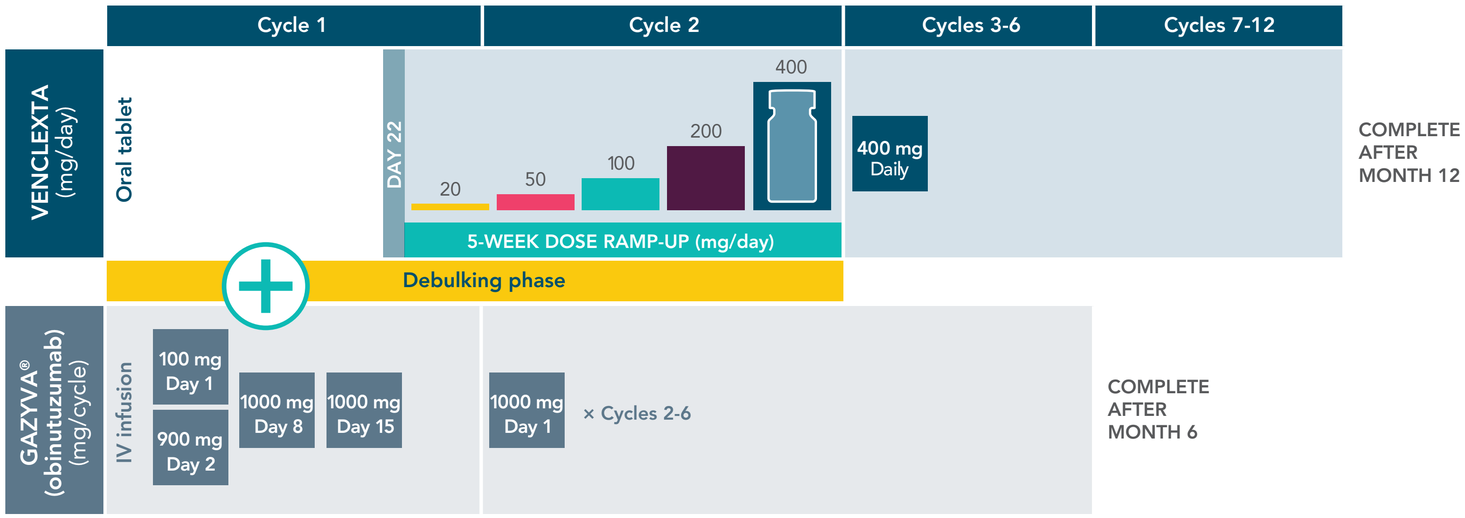
Please see additional Important Safety Information on pages 19 and 20.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

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

Previously Untreated CLL

The only chemo-free regimen designed to stop treatment at 1 year in previously untreated CLL[1]

VEN+G for previously untreated CLL



Graphic not to scale. Each cycle is 28 days.

VENCLEXTA

- Tumor burden assessments, including radiographic evaluation, and blood chemistry assessments, are recommended prior to VENCLEXTA initiation to assess the risk of TLS
- On Cycle 1, Day 22, start VENCLEXTA according to the dose 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

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 Cycles 2–6
- See pages 5-8 for an overview of GAZYVA dosing and administration

Important Safety Information

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Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. 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. TLS, including fatal cases, has been reported after a single 20 mg dose.
- In patients with CLL/SLL 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/SLL monotherapy trials. 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.

VEN+G=VENCLEXTA + GAZYVA; IV=intravenous; TLS=tumor lysis syndrome; ALC=absolute lymphocyte count.

Please see additional Important Safety Information on pages 19 and 20.
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Previously Untreated CLL

The only chemo-free regimen designed to stop treatment at 1 year in previously untreated CLL[1]

VEN+G for previously untreated CLL

Cycle 1	Cycle 2	Cycles 3-6	Cycles 7-12

98%
MEDIAN ALC REDUCTION

After the first treatment cycle of GAZYVA® (obinutuzumab) and before the VENCLEXTA dose ramp-up, median ALC was reduced by 98%[1,4]

- Per the trial protocol, tumor burden was assessed based on ALC and lymph node size.[1] The effect of the first GAZYVA treatment cycle on lymph node size was not evaluated.[4] The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up; median lymphocyte count was reduced in the safety evaluable population (N=212) from 55 × 10^9 cells/L at baseline to 1.27 × 10^9 cells/L at Day 15. Median lymphocyte counts are descriptive in nature and were not powered for any type of comparison. Changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators

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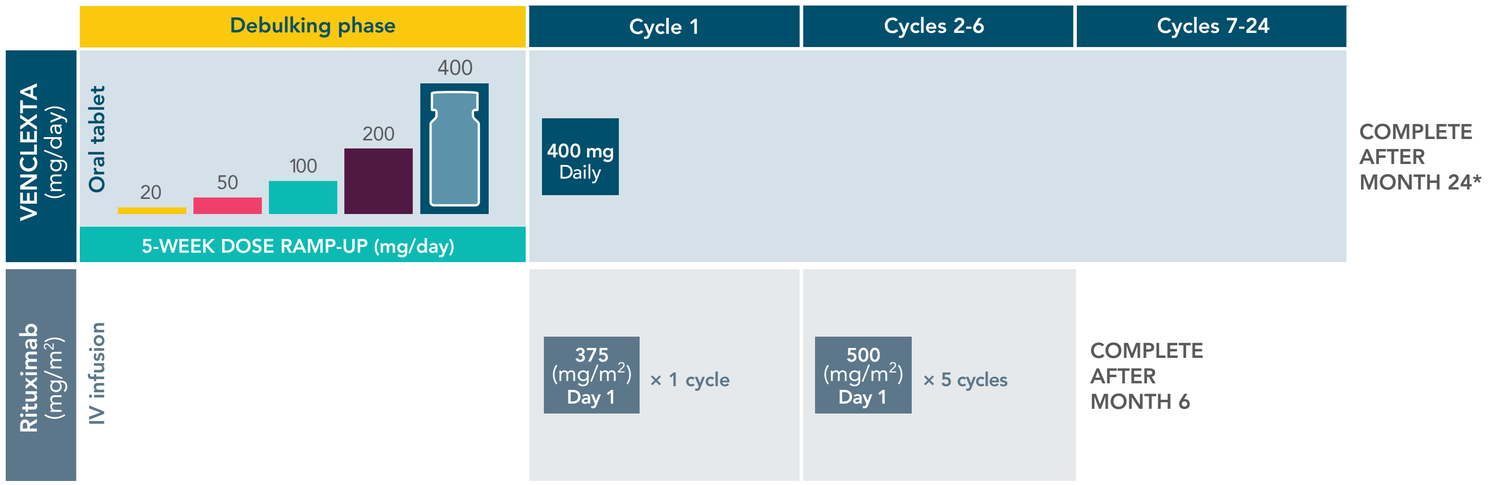
VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

R/R CLL

The only chemo-free, oral-based regimen designed to stop treatment at 2 years* in R/R CLL[1]

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



Graphic not to scale. Each cycle is 28 days.

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

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

VENCLEXTA

- Tumor burden assessments, including radiographic evaluation and blood chemistry assessments, are recommended prior to VENCLEXTA initiation to assess the risk for TLS
- 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

- Administer rituximab 375 mg/m^2 on Day 1 of Cycle 1, after the patient has received the 400 mg dose of VENCLEXTA for 7 days
- Administer rituximab 500 mg/m^2 on Day 1 of Cycles 2–6
- Refer to rituximab Prescribing Information for more information about recommended dosing

IRR=infusion-related reaction.

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

Important Safety Information (cont'd)

Tumor Lysis Syndrome (cont'd)

- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.
- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

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

GAZYVA® (obinutuzumab) dosing and administration overview[5]

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	• Administer at 25 mg/hr over 4 hours • Do not increase the infusion rate
	Day 2	900 mg	• If no infusion-related reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr • If an infusion-related reaction occurred during the previous infusion, administer at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 8	1000 mg	• If no infusion-related 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/hr • If an infusion-related 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	

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible and adjust dosing schedule to maintain the time interval between doses. If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose.

Important dosing information

- 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 IRRs that can be fatal if they occur

IRR=infusion-related reaction.

Important Safety Information for GAZYVA

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, including BOXED WARNINGS, for GAZYVA on page 9. Please see accompanying full Prescribing Information for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

GAZYVA® (obinutuzumab) dosing and administration overview (cont'd)[5]

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 × 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 IRRs.

†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

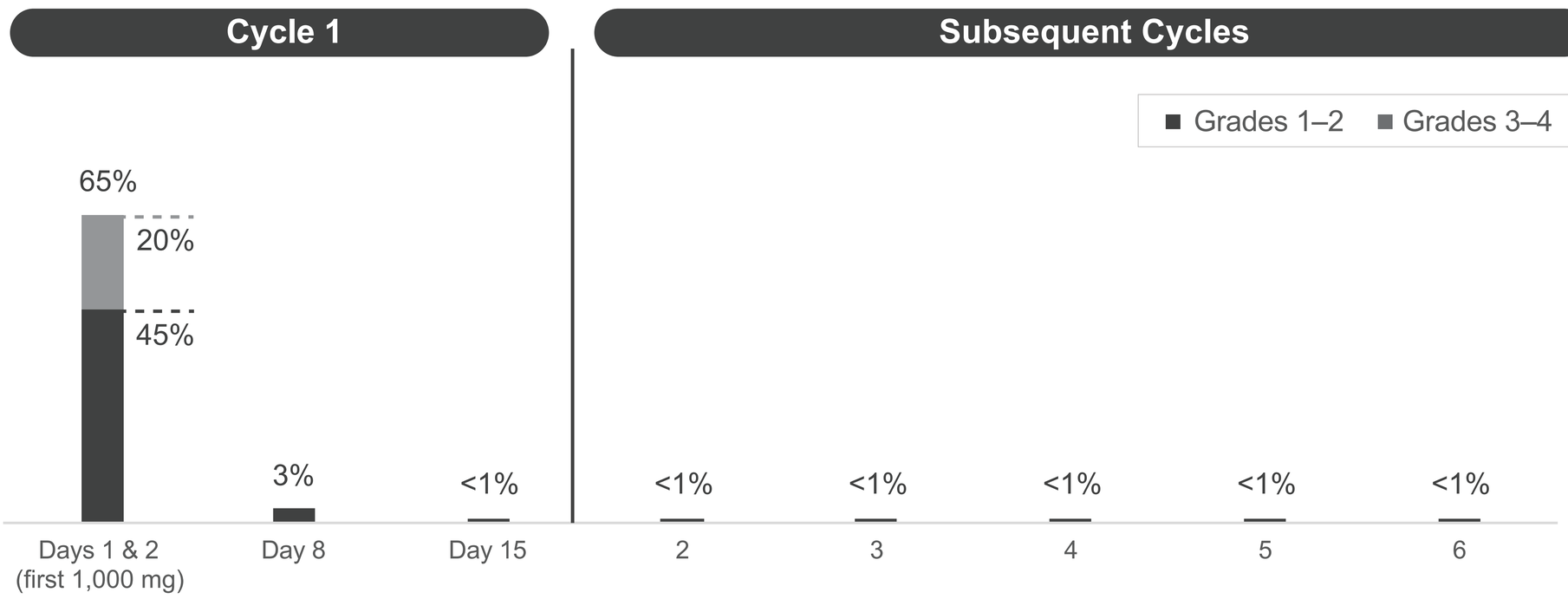
- Patients with preexisting cardiac or pulmonary conditions may be at greater risk of experiencing more severe IRRs
- Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here
- Patients with high tumor burden, high circulating absolute lymphocyte count (>25 × 10^9/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 for patients with severe and long lasting (>1 week) neutropenia

Please see full Important Safety Information, including BOXED WARNINGS, for GAZYVA on page 9. Please see accompanying full Prescribing Information for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

GAZYVA® (obinutuzumab) incidence of infusion-related reactions (IRRs)[2,5,6]

The incidence of IRRs in the CLL11 study was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 IRRs was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1,000 mg and < 1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1,000 mg infused.[5]

Rates of IRRs by cycle[5]



Of the first 53 patients receiving GAZYVA in CLL11, 47 (89%) experienced an IRR. After this experience, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on day 1 and 900 mg on day 2). For the 140 patients for whom these mitigation measures were implemented, 74 patients (53%) experienced a reaction with the first 1,000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and < 3% thereafter.

Overall IRR rates (across all 6 cycles), by trial

	CLL11 (Stage 2)[5]	CLL14[2,6]	
	GClb (N=336)	VEN+G (N=212)	GClb (N=214)
All Grades, %	66	44.8	51.4
Grade 3–4, %	20	9	10.3

Dosing and administration of obinutuzumab in CLL14 were aligned with instructions within the GAZYVA Prescribing Information.
IRR rates by cycle in CLL14 were not analyzed.

Please see full Important Safety Information, including BOXED WARNINGS, for GAZYVA on page 9. Please see accompanying full Prescribing Information for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

GAZYVA® (obinutuzumab) dosing and administration overview (cont'd)[5]

Adjusting infusions in case of IRRs

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

IRRs	Recommendations per prescribing information
Grade 4 (life-threatening)	Stop infusion immediately and permanently discontinue GAZYVA therapy.
Grade 3 (severe)	Interrupt infusion and manage symptoms. • 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 IRR occurred) and, if patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose • Permanently discontinue treatment if patients experience a Grade 3 IRR at rechallenge – 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 manage symptoms. • Upon resolution of symptoms, continue or resume GAZYVA infusion and, if patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose – 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. IRRs within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed

Please see full Important Safety Information, including BOXED WARNINGS, for GAZYVA on page 9. Please see accompanying full Prescribing Information for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

Important Safety Information for GAZYVA® (obinutuzumab)

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-Related Reactions:** Premedicate patients with glucocorticoid, acetaminophen, and antihistamine. Monitor patients closely during infusions. Interrupt, reduce rate, or discontinue for infusion-related reactions based on severity
- **Hypersensitivity Reactions Including Serum Sickness:** Discontinue GAZYVA permanently
- **Tumor Lysis Syndrome (TLS):** Premedicate with antihyperuricemics 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:** Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection
- **Neutropenia:** In patients with Grade 3 to 4 neutropenia, monitor laboratory tests until resolution and for infection. Consider dose delays and infection prophylaxis, as appropriate
- **Thrombocytopenia:** Monitor for decreased platelet counts and bleeding. Transfusion may be necessary
- **Disseminated Intravascular Coagulation:** Evaluate cause and monitor for bleeding, thrombosis, and need for supportive care
- **Immunization:** Avoid administration of live virus vaccines during GAZYVA treatment and until B-cell recovery
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception

Additional Important Safety Information

- The most common adverse reactions (incidence ≥20% and ≥2% greater in the GAZYVA treated arm) observed in patients with CLL were infusion-related reactions (66%), and neutropenia (38%)

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, for GAZYVA or visit https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

Initiating VENCLEXTA[1]

Assess blood chemistry and correct pre-existing abnormalities prior to initiation of treatment:

- Potassium
- Uric acid
- Phosphorus
- Calcium
- Creatinine

Considerations for TLS with VENCLEXTA

- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption (see dose modification and interruption information on pages 14 and 15)
- 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
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function (CrCl <80 mL/min) and tumor burden; splenomegaly may also increase the risk
- Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule
- The risk of TLS may decrease as tumor burden decreases
- Reassess the risk of TLS when reinitiating VENCLEXTA after a dosage interruption lasting more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up. Institute prophylaxis and monitoring as needed

Appropriate prophylaxis can help lower the risk of TLS.

3 STEPS: ASSESS, PREPARE, INITIATE

	LOW TUMOR BURDEN	**MEDIUM** TUMOR BURDEN	**HIGH** TUMOR BURDEN
STEP 1: **ASSESS** Prior to initiation	All lymph nodes (LN) <5 cm **AND** Absolute lymphocyte count (ALC) <25 x 10^9/L	Any LN 5 cm to <10 cm **OR** ALC ≥25 x 10^9/L	Any LN ≥10 cm **OR** Any LN ≥5 cm and ALC ≥25 x 10^9/L
STEP 2: **PREPARE**	**Oral hydration*:** 1.5–2 L **Allopurinol†**	**Oral hydration*:** 1.5–2 L **IV hydration:** Consider for patients with medium tumor burden **Allopurinol†**	**Oral hydration*:** 1.5–2 L **IV hydration:** 150–200 mL/hr as tolerated **Allopurinol†** **Rasburicase[6]:** Consider for elevated uric acid (>8 mg/dL)
STEP 3: **INITIATE** And monitor blood chemistry‡§ for first dose of each ramp-up week	OUTPATIENT		HOSPITAL / OUTPATIENT

OUTPATIENT

Day 1, Week:	1	2	3	4	5
Dosage	20 mg	50 mg	100 mg	200 mg	400 mg
Blood chemistry labs: Pre-Dose	☐	☐	☐	☐	☐
Blood chemistry labs: 6–8 Hours	☐	☐	—	—	—
Blood chemistry labs: 24 Hours	☐	☐	—	—	—

For the first doses of 20 mg and 50 mg, consider hospitalization for patients with medium tumor burden and CrCl <80 mL/min; for these patients, see table to the right for monitoring in hospital.

HOSPITAL / OUTPATIENT

Day 1, Week:	1	2	3	4	5
Dosage	20 mg	50 mg	100 mg	200 mg	400 mg
Blood chemistry labs: Pre-Dose	☐	☐	☐	☐	☐
Blood chemistry labs: 4 Hours	☐	☐	—	—	—
Blood chemistry labs: 8 Hours	☐	☐	☐	☐	☐
Blood chemistry labs: 12 Hours	☐	☐	—	—	—
Blood chemistry labs: 24 Hours	☐	☐	☐	☐	☐

*1.5–2 L of water (~56 ounces) should be consumed every day starting at least 2 days before the first dose and throughout the ramp-up phase, especially on the first day of each dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

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

‡Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

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

CrCl=creatinine clearance.

Important Safety Information (cont'd)

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 when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia and resume at same or reduced dose. Consider supportive measures including antimicrobials and 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 for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Please see additional Important Safety Information on pages 19 and 20.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

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

Confidently start treatment with VENCLEXTA regimens[1]

PATIENTS WITH LOW OR MEDIUM TUMOR BURDEN MAY BE INITIATED IN THE OUTPATIENT SETTING

- Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule
- Follow the Assess, Prepare, Initiate table on page 10 for recommended TLS prophylaxis based on tumor burden
- Patients who may be initiated in the outpatient setting:
  - **Low tumor burden:** those with all lymph nodes (LN) <5 cm and an absolute lymphocyte count (ALC) <25 × 10^9/L
  - **Medium tumor burden:** those with any LN from 5 cm to <10 cm or an ALC ≥25 × 10^9/L
- For the first doses of 20 mg and 50 mg, consider hospitalization for patients with medium tumor burden and CrCl <80 mL/min
- Patients with high tumor burden—those with any LN ≥10 cm or those with ALC ≥25 ×10^9/L and any LN ≥5 cm—should be initiated in the hospital
- In the CLL14 and MURANO clinical trials, TLS risk category was determined based on lymph node size, ALC, and investigator discretion[1,6,7]
  - Baseline characteristics in the CLL14 trial: 13% (29/216) of VEN+G patients had low, 64% (139/216) had medium, and 22% (48/216) had high TLS risk[4]
  - Baseline characteristics in the MURANO trial: 18% (34/194) of VEN+R patients had low, 55% (106/194) had medium, and 28% (54/194) had high TLS risk[8]
- In the CLL14 trial, after the first treatment cycle of GAZYVA® (obinutuzumab) and before the VENCLEXTA dose ramp-up, median ALC was reduced by 98%[1,4]
  - 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. The trial started with an initial cycle of GAZYVA followed by the 5-week VENCLEXTA dose ramp-up; median lymphocyte count was reduced in the safety evaluable population (N=212) from 55 × 10^9 cell/L at baseline to 1.27 × 10^9 cell/L at Day 15. Median lymphocyte counts are descriptive in nature and were not powered for any type of comparison. Changes in TLS risk status based on ALC reduction were at the discretion of the trial investigators

DOSE RAMP-UP IS DESIGNED TO GRADUALLY REDUCE TUMOR BURDEN (DEBULK) AND DECREASE THE RISK OF TLS[1]

- **TLS prophylaxis and monitoring protocols can reduce the risk of TLS**
- **In the CLL14 trial, the incidence of laboratory TLS was 1%** (3/212) in patients treated with VEN+G. **The incidence of clinical TLS was 0%**[1,4]
  - All 3 events of TLS occurred during treatment with GAZYVA, before treatment initiation with VENCLEXTA. All 3 events of TLS resolved and did not lead to withdrawal from the trial. GAZYVA administration was delayed in 2 cases in response to the TLS events[1,4]
- **In the MURANO trial, the incidence of TLS was 3% overall** (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures. **The incidence of clinical TLS was 0%** in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures
  - All events of TLS occurred during the VENCLEXTA 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

Important Safety Information (cont'd)

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 use effective contraception during treatment and for 30 days after the last dose.

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.

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How VENCLEXTA is taken[1]

Advise patients to:

- ✔ Take VENCLEXTA tablets exactly as they are prescribed and not to change or interrupt their dose unless they are told to do so by their doctor.
- ✔ Take VENCLEXTA orally once daily, at approximately the same time each day, according to their HCP's instructions and that the tablets should be swallowed whole with a meal and water without being chewed, crushed, or broken.
- ✔ Be adequately hydrated every day they take 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.
- ✔ Attend every scheduled appointment for blood work or other laboratory tests.

Advise patients NOT to:

- ✖ Crush, chew, or break their VENCLEXTA tablets.
- ✖ Remove their VENCLEXTA tablets from the original packaging during the first 4 weeks of treatment, or transfer them to a different container.
- ✖ Take an additional dose if vomiting occurs after taking VENCLEXTA. They should take the next dose at the usual time the following day.
- ✖ Consume grapefruit products, Seville oranges, or 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.

By more than 8 hours, the patient should not take the missed dose and should take the next dose at the usual time.

Important Safety Information (cont'd)

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 (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.
- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). 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 the last rituximab were reported in 2% (4/194) of patients.

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EXAMPLE OF TREATMENT INITIATION CALENDAR FOR VENCLEXTA

LOW OR MEDIUM TUMOR BURDEN[1]

This example is provided to help you in using the full Prescribing Information and is for illustrative purposes only. No two patients are 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

Assess tumor burden, renal function and comorbidities, and blood chemistries.
Correct pre-existing abnormalities prior to VENCLEXTA initiation.

STEP 2: PREPARE

2–3 DAYS PRIOR TO VENCLEXTA INITIATION	AT LEAST 2 DAYS PRIOR TO VENCLEXTA INITIATION	BEFORE EACH DOSE INCREASE
Start allopurinol*	Start oral/IV hydration	Pre-dose labs

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

STEP 3: INITIATE

WEEK 1

20 mg

Take two 10-mg tablets once daily

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
6-8 HOUR POST-DOSE LABS	24-HOUR POST-DOSE LABS					PRE-DOSE LABS BEFORE NEXT DOSE
10 mg ×2	10 mg ×2	10 mg ×2	10 mg ×2	10 mg ×2	10 mg ×2	10 mg ×2

WEEK 2

50 mg

Take one 50-mg tablet once daily

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
6-8 HOUR POST-DOSE LABS	24-HOUR POST-DOSE LABS					PRE-DOSE LABS BEFORE NEXT DOSE
50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg

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
Reminder: Order bottle of 100-mg tablets—Dosing for Week 5+						PRE-DOSE LABS BEFORE NEXT DOSE
100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

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
100 mg ×2	100 mg ×2	100 mg ×2	100 mg ×2	100 mg ×2	100 mg ×2	100 mg ×2

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
100 mg ×4	100 mg ×4	100 mg ×4	100 mg ×4	100 mg ×4	100 mg ×4	100 mg ×4

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

Advise patients to drink 1.5–2 L (~56 ounces) of water daily while taking VENCLEXTA.

*Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.[1]

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Dose modifications or interruptions can help manage select adverse reactions[1]

Interrupt dosing or reduce dose for select adverse reactions

- For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of the 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 (e.g., all or some levels of the ramp-up schedule)

Recommended VENCLEXTA dose modifications for adverse reactions*	
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 the dose-reduction guidelines on page 15.
	For any events of clinical TLS,† resume at a reduced dose following resolution. See the dose-reduction guidelines on page 15.
Nonhematologic adverse reactions	
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.
2nd occurrence: Grade 3 or 4 nonhematologic toxicities	Interrupt VENCLEXTA. Follow dose-reduction guidelines on page 15 when resuming VENCLEXTA treatment after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic adverse reactions	
1st occurrence: Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
2nd occurrence: Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia)	Interrupt VENCLEXTA. Follow dose-reduction guidelines on page 15 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.

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Dose reduction for adverse reactions during VENCLEXTA treatment[1]

Dose reduction for adverse reactions 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.

†If a dosage interruption lasts more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up, reassess the risk of TLS and determine if reinitiation at a reduced dosage is necessary.

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.

- 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 adverse reactions

CYP3A=cytochrome P450 3A; P-gp=P-glycoprotein.

Drug Interactions Brochure

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Previously Untreated CLL

Summary of VEN+G safety data[1]

VEN+G safety from the CLL14 trial

- The median duration of exposure to VENCLEXTA was 10.5 months (range: 0–13.5 months). The median number of cycles was 6 for GAZYVA® (obinutuzumab)
- In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection, compared with 1% (3/214) of patients in the GClb arm[1,4]
- Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each)

Adverse reactions (≥10%) in patients treated with VEN+G

	VEN+G (N=212)		GClb (N=214)	
Adverse Reaction by Body System	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
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.

Rates of discontinuation, dose reduction, and dose interruption

- In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 21%, and dose interruption in 74%
- Neutropenia led to discontinuation of VENCLEXTA in 2% of patients, dose reduction in 13%, and dose interruption in 41%

For 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 adverse reaction that occurred in ≥10% of patients was neutropenia (26%)
- The Grade ≥3 adverse reactions that occurred in ≥2% of patients were neutropenia (23%) and anemia (2%)

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R/R CLL

Summary of VEN+R safety data[1]

VEN+R safety from MURANO trial

- 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
- 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 last rituximab treatment 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%)
- 93% (173/187) of patients in the VEN+R arm and 68% (127/188) of patients in the BR arm completed 6 combination treatment cycles[8]
  - 7 patients in each arm did not receive combination therapy: In the VEN+R arm, 7 patients did not receive rituximab, and in the BR arm, 7 patients did not receive either bendamustine or rituximab[3]
  - Patients needed to receive at least 90% of the target dose to be counted as receiving a full cycle[8]

Adverse reactions (≥10%) in patients treated with VEN+R

	VEN+R (N=194)		BR (N=188)	
Adverse Reaction by Body System	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Blood and lymphatic system disorders				
Neutropenia*	65	62	50	44
Anemia*	16	11	23	14
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Nausea	21	1	34	1
Constipation	14	<1	21	0
Infections and infestations				
Upper respiratory tract infection*	39	2	23	2
Lower respiratory tract infection*	18	2	10	2
Pneumonia*	10	7	14	10
General disorders and administration site conditions				
Fatigue*	22	2	26	<1

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

Rates of discontinuation, dose reduction, and dose interruption

- In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%
- Neutropenia led to discontinuation of VENCLEXTA in 3% of patients and dose interruption in 46%. Thrombocytopenia led to discontinuation in 3% of patients

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

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

- Adverse reactions that occurred in ≥10% of patients were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infection (11%)
- The Grade 3 or 4 adverse reactions that occurred in ≥2% of patients were neutropenia (12%) and anemia (3%)

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Connect patients with helpful resources after VENCLEXTA has been prescribed

Patient support programs

Serious illnesses can come with many challenges. Getting VENCLEXTA shouldn't be one of them. We believe every person should get the VENCLEXTA they have been prescribed, and we offer programs to help make this happen.

If your patients:

Need help understanding their insurance coverage and related financial responsibilities, **VENCLEXTA Access Solutions** is here to help. Call **(888) 249-4918** for more information.

Do not have insurance coverage or have financial concerns and meet certain eligibility criteria, the **Genentech Patient Foundation** may be able to provide free medicine.*†

Have insurance and need help paying for their medicine, **Affordability Options** may be available:

- The **Genentech Co-pay Assistance Program** provides financial assistance to eligible commercially insured patients to help with their OOP costs‡
- We can help refer patients to **independent co-pay assistance foundations** that may be able to help commercially or publicly insured patients afford their medicines§

The Genentech Patient Resource Center can help answer questions and connect you to the right VENCLEXTA patient support program. Call (877) 436-3683 to get started.

*To be eligible for free VENCLEXTA from the Genentech Patient Foundation, insured patients who have coverage for their medicine should try to pursue other forms of financial assistance, if available, and meet certain income requirements. Uninsured patients and insured patients without coverage for their medicine must meet a different set of income requirements.

†Genentech reserves the right to modify or discontinue the program at any time and to verify the accuracy of the information submitted.

‡Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their medications and/or administration of their Genentech medication. Patient must be taking the Genentech medication for an FDA-approved indication. Please visit the Co-pay Program website for the full list of Terms and Conditions.

§Independent co-pay assistance foundations have their own rules for eligibility. Genentech and AbbVie have no involvement or influence in independent foundation decision-making or eligibility criteria and do not know if a foundation will be able to help your patient. We can only refer your patient to a foundation that supports their disease state. The information is provided as a resource for you. Genentech and AbbVie do not endorse or show preference for any particular foundation. The foundations to which we refer your patient may not be the only ones that might be able to help.

OOP=out of pocket.

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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 treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. 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. TLS, including fatal cases, has been reported after a single 20 mg dose.
- In patients with CLL/SLL 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/SLL monotherapy trials. 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.
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.
- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

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 when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia and resume at same or reduced dose. Consider supportive measures including antimicrobials and 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 for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

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 use effective contraception during treatment and for 30 days after the last dose.

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.

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Important Safety Information for VENCLEXTA (cont'd)

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 (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.
- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). 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 the last rituximab were reported in 2% (4/194) of patients.
- **In patients with CLL/SLL receiving monotherapy,** the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥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%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A 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.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.
- 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.

Lactation

- Advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

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

Hepatic Impairment

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

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VENCLEXTA Patient Support Programs

VENCLEXTA Access Solutions

Your helpful resource for access and reimbursement support

(866) 422-2377 | **Genentech-Access.com/VENCLEXTA**

The Genentech Oncology Co-pay Assistance Program

Genentech co-pay programs provide financial assistance to eligible commercially insured patients to help with their co-pays, co-insurance, or other out-of-pocket (OOP) costs*

(855) MY-COPAY/(855) 692-6729 | **CopayAssistanceNow.com**

*Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their medications and/or administration of their Genentech medication. Patient must be taking the Genentech medication for an FDA-approved indication. See full Terms and Conditions at CopayAssistanceNow.com.

Contact your AbbVie or Genentech representative

to learn more about VENCLEXTA or ask questions about treatment initiation

Learn about ways to manage TLS, including monitoring, prophylaxis, and a tumor burden assessment tutorial.

Watch a certified Physician Assistant discuss how to start VENCLEXTA.

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References: 1. VENCLEXTA Prescribing Information. **2.** Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236. **3.** Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12):1107-1120. **4.** Data on file, AbbVie Inc. ABVRRTI69608. **5.** GAZYVA Prescribing Information. **6.** Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23) (suppl appendix). **7.** Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12) (suppl appendix). **8.** Data on file, AbbVie Inc. ABVRRTI69609.

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