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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VENCLEXTA safely and effectively. See full prescribing information for VENCLEXTA.

VENCLEXTA® (venetoclax tablets) for oral use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage, CLL (1.1)	05/2019
Indications and Usage, AML (1.2)	11/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4)	05/2019
Warnings and Precautions, Neutropenia (5.2)	11/2018
Warnings and Precautions, Infections (5.3)	05/2019

INDICATIONS AND USAGE

VENCLEXTA is a BCL-2 inhibitor indicated:
- For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.1)
- In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
  This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.2)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for recommended VENCLEXTA starting and ramp-up dosages. (2.1)
- VENCLEXTA tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets. (2.1)
- Perform prophylaxis for tumor lysis syndrome. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 50 mg, 100 mg (3)

CONTRAINDICATIONS

Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL/SLL is contraindicated. (2.4, 4, 7.1)

WARNINGS AND PRECAUTIONS

- Tumor Lysis Syndrome (TLS): Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. (2.2, 5.1)
- Neutropenia: Monitor blood counts and for signs of infection; manage as medically appropriate. (2.3, 5.2)
- Infections: Monitor for signs and symptoms of infection and treat promptly. Withhold treatment for Grade 3 and higher infection until resolution. (5.3)
- Immunization: Do not administer live attenuated vaccines prior to, during, or after VENCLEXTA treatment. (5.4)
- Embryo-Fetal Toxicity: May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment. (5.5)

ADVERSE REACTIONS

In CLL/SLL, the most common adverse reactions (≥20%) for VENCLEXTA when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema (6.1).

In AML, the most common adverse reactions (≥30%) in combination with azacitidine or decitabine or low-dose cytarabine were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A inhibitors or P-gp inhibitors: Adjust dosage of VENCLEXTA. (2.4, 7.1)
- Strong or moderate CYP3A inducers: Avoid co-administration. (7.1)
- P-gp substrates: Take at least 6 hours before VENCLEXTA. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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Exhibit 2027
Apotex v. Agios
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Ex. 2027-001

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

1.2 Acute Myeloid Leukemia

VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

This indication is approved under accelerated approval based on response rates *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA dosing begins with a 5-week ramp-up.

VENCLEXTA 5-week Dose Ramp-Up Schedule

Administer the VENCLEXTA dose according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg as shown in Table 1. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

Table 1. Dosing Schedule for Ramp-Up Phase in Patients with CLL/SLL

	VENCLEXTA Daily Dose
Week 1	20 mg
Week 2	50 mg

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Week 3	100 mg
Week 4	200 mg
Week 5 and beyond	400 mg

The CLL/SLL Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule. The 400 mg dose is achieved using 100 mg tablets supplied in bottles *[see How Supplied/Storage and Handling (16)]*.

VENCLEXTA in Combination with Obinutuzumab

Start obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2. Administer 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. Refer to the obinutuzumab prescribing information for recommended obinutuzumab dosing information.

On Cycle 1 Day 22, start VENCLEXTA according to the 5-week ramp-up schedule (see Table 1). 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.

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the 5-week dose ramp-up schedule with VENCLEXTA (see Table 1) and has received the 400 mg dose of VENCLEXTA for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, with rituximab dosed at 375 mg/m^2 intravenously for Cycle 1 and 500 mg/m^2 intravenously for Cycles 2-6.

Patients should continue VENCLEXTA 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab.

VENCLEXTA as Monotherapy

The recommended dose of VENCLEXTA is 400 mg once daily after the patient has completed the 5-week dose ramp-up schedule. VENCLEXTA should be taken orally once daily until disease progression or unacceptable toxicity is observed.

Acute Myeloid Leukemia

The dose of VENCLEXTA depends upon the combination agent.

The VENCLEXTA dosing schedule (including ramp-up) is shown in Table 2. Initiate the azacitidine or decitabine or low-dose cytarabine on Day 1.

Table 2. Dosing Schedule for Ramp-up Phase in Patients with AML

	VENCLEXTA Daily Dose
Day 1	100 mg
Day 2	200 mg
Day 3	400 mg

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Days 4 and beyond	400 mg when dosing in combination with **azacitidine or decitabine**	600 mg when dosing in combination with **low-dose cytarabine**

Continue VENCLEXTA, in combination with azacitidine or decitabine or low-dose cytarabine, until disease progression or unacceptable toxicity is observed.

2.2 Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

Patients treated with VENCLEXTA may develop tumor lysis syndrome. Refer to the appropriate section below for specific details on management. Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week 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.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (creatinine clearance [CLcr] <80 mL/min) further increases the risk. Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA. The risk may decrease as tumor burden decreases *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

Table 3 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumor burden determination from clinical trial data. Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule.

Table 3. Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL/SLL

Tumor Burden		**Prophylaxis**		**Blood Chemistry Monitoring[c,d]**
		Hydration[a]	**Anti-hyperuricemics**	**Setting and Frequency of Assessments**
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours

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				• For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 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 <80ml/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	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 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CLcr = creatinine clearance; LN = lymph node.
[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Acute Myeloid Leukemia

- All patients should have white blood cell count less than 25 × 10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required.
- Prior to first VENCLEXTA dose, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents and continue during ramp-up phase.

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- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

2.3 Dose Modifications Based on Toxicities

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Interrupt dosing or reduce dose for toxicities. See Table 4 and Table 5 for recommended dose modifications for toxicities related to VENCLEXTA. 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 for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule) *[see Dosage and Administration (2.1, 2.2)]*.

Table 4. Recommended VENCLEXTA Dose Modifications for Toxicities[a] in CLL/SLL

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 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 Table 5) *[see Dosage and Administration (2.2)]*.
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5) *[see Dosage and Administration (2.2)]*.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	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	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.

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Hematologic Toxicities		
Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	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	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA 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. [a]Adverse reactions were graded using NCI CTCAE version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures *[see Adverse Reactions (6.1)]*.		

Table 5. Dose Reduction for Toxicity During VENCLEXTA Treatment in CLL/SLL

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10
[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.	

Acute Myeloid Leukemia

Monitor blood counts frequently through resolution of cytopenias. Management of some adverse reactions *[see Warnings and Precautions (5.2)* and *Adverse Reactions (6.2)]* may require dose interruptions or permanent discontinuation of VENCLEXTA. Table 6 shows the dose modification guidelines for hematologic toxicities.

Table 6. Recommended Dose Modifications for Toxicities[a] in AML

Event	Occurrence	Action
Hematologic Toxicities		

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Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia *[see Warnings and Precautions (5.2)]*	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent treatment cycle of VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine or decitabine or low-dose cytarabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of VENCLEXTA and azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose and the duration reduced by 7 days for each subsequent cycle.
[a]Adverse reactions were graded using NCI CTCAE version 4.0.		

2.4 Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Table 7 describes VENCLEXTA contraindication or dosage modification based on concomitant use with a strong or moderate CYP3A inhibitor or P-gp inhibitor *[see Drug Interactions (7.1)]* at initiation, during, or after the ramp-up phase.

Resume the VENCLEXTA dosage 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 *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

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Table 7. 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)[a]
Posaconazole	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 70 mg.
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	
Other strong CYP3A inhibitor	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 100 mg.
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	
Moderate CYP3A inhibitor	Reduce the VENCLEXTA dose by at least 50%.		
P-gp inhibitor			

[a]In patients with CLL/SLL, consider alternative medications or reduce the VENCLEXTA dose as described in Table 7.

2.5 Missed Dose

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

3 DOSAGE FORMS AND STRENGTHS

Table 8. VENCLEXTA Tablet Strength and Description

Tablet Strength	Description of Tablet
10 mg	Round, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “10” on the other side
50 mg	Oblong, biconvex shaped, beige film-coated tablet debossed with “V” on one side and “50” on the other side
100 mg	Oblong, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “100” on the other side

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4 CONTRAINDICATIONS

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 tumor lysis syndrome *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA *[see Adverse Reactions (6.1, 6.2)]*.

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 *[see Adverse Reactions (6.1)]*.

VENCLEXTA can cause rapid reduction in tumor and thus 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.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases *[see Dosage and Administration (2.2, 2.3) and Use in Specific Populations (8.6)]*.

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and requires VENCLEXTA dose adjustment *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]*.

5.2 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 (see Tables 10, 12, 14). Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies *[see Adverse Reactions (6.1)]*.

In patients with AML, baseline neutrophil counts worsened in 97% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy.

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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) *[see Dosage and Administration (2.3)]*.

5.3 Infections

Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA *[see Adverse Reactions (6.1)]*. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection *[see Dosage and Administration (2.3)]*.

5.4 Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Advise patients that vaccinations may be less effective.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at a dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant women using VENCLEXTA. Advise females of reproductive potential to avoid pregnancy during treatment. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Tumor Lysis Syndrome *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience with CLL/SLL

<u>CLL14</u>

The safety of VENCLEXTA in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) was evaluated in a randomized, open-label, actively controlled trial in patients with previously untreated CLL. Patients randomized to the VEN+G

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arm were treated with VENCLEXTA and obinutuzumab in combination for six cycles, then with VENCLEXTA as monotherapy for an additional six cycles. Patients initiated the first dose of the 5 week ramp-up for VENCLEXTA on Day 22 of Cycle 1 and once completed, continued VENCLEXTA 400 mg once daily for a total of 12 cycles. Details of the study treatment are described in Section 14 *[see Clinical Studies (14.1)]*. The trial required a total Cumulative Illness Rating Scale (CIRS) >6 or CLcr <70 mL/min, hepatic transaminases and total bilirubin ≤2 times upper limit of normal, and excluded patients with any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system.

A total of 426 patients were treated (212 with VEN+G, 214 with GClb). 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.

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. Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each).

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

Table 9 and Table 10 present adverse reactions and laboratory abnormalities identified in the CLL14 trial, respectively. The most common (≥15%) adverse reactions observed with VEN+G were neutropenia, diarrhea, fatigue, nausea, anemia, and upper respiratory tract infection.

Table 9: Common (≥10%) Adverse Reactions in Patients Treated with VEN+G

Adverse Reaction by Body System	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Blood & lymphatic system disorders				
Neutropenia[a]	60	56	62	52
Anemia[a]	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[a]	21	2	23	1
Infections and Infestations				
Upper respiratory tract infection[a]	17	1	17	1

[a]Includes multiple adverse reaction terms.

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Other clinically important adverse reactions (all Grades) reported in <10% of patients treated with VEN+G are presented below:

Blood & lymphatic system disorders: febrile neutropenia (6%)

Infection and infestations (all include multiple adverse reaction terms): pneumonia (9%), urinary tract infection (6%), sepsis (4%)

Metabolism and nutrition disorder: tumor lysis syndrome (1%)

During treatment with single agent VENCLEXTA after completion of VEN+G combination treatment, the most common all grade adverse reaction (≥10% patients) reported was neutropenia (26%). The most common grade ≥3 adverse reactions (≥2% patients) were neutropenia (23%), and anemia (2%).

Table 10: New or Worsening Clinically Important Laboratory Abnormalities Occurring at ≥10% in Patients Treated with VEN+G

	VENCLEXTA + Obinutuzumab (N = 212)		**Obinutuzumab + Chlorambucil (N = 214)**	
Laboratory Abnormality[a]	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Leukopenia	90	46	89	41
Lymphopenia	87	57	87	51
Neutropenia	83	63	79	56
Thrombocytopenia	68	28	71	26
Anemia	53	15	46	11
Chemistry				
Blood creatinine increased	80	6	74	2
Hypocalcemia	67	9	58	4
Hyperkalemia	41	4	35	3
Hyperuricemia	38	38	38	38

[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.

Grade 4 laboratory abnormalities developing in ≥2% of patients treated with VEN+G include neutropenia (32%), leukopenia and lymphopenia (10%), thrombocytopenia (8%), hypocalcemia (8%), hyperuricemia (7%), blood creatinine increased (3%), hypercalcemia (3%), and hypokalemia (2%).

MURANO

The safety of VENCLEXTA in combination with rituximab (VEN+R) versus bendamustine in combination with rituximab (B+R), was evaluated in an open-label randomized study, in patients with CLL who had received at least one prior therapy.

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Patients randomized to VEN+R completed the scheduled ramp-up (5 weeks) and received VENCLEXTA 400 mg once daily in combination with rituximab for 6 cycles followed by single agent VENCLEXTA for a total of 24 months after ramp-up. Patients randomized to B+R received 6 cycles (28 days per cycle) for a total of 6 months. Details of the study treatment are described in Section 14 *[see Clinical Studies (14.1)]*.

At the time of analysis, the median duration of exposure was 22 months in the VEN+R arm compared with 6 months in the B+R 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 were reported in 2% (4/194) of patients. Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with most frequent (≥5%) being pneumonia (9%).

In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%. In the B+R arm, adverse reactions led to treatment discontinuation in 10% of patients, dose reduction in 15%, and dose interruption in 40%. 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.

Table 11 and Table 12 present adverse reactions and laboratory abnormalities, respectively, identified in the MURANO trial. The MURANO trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for VEN+R as compared with B+R, for any specific adverse reaction or laboratory abnormality.

Table 11. Common (≥10%) Adverse Reactions Reported with ≥5% Higher All-Grade or ≥2% Higher Grade ≥3 Incidence in Patients Treated with VEN+R Compared with B+R

	VENCLEXTA + Rituximab Followed by Single Agent VENCLEXTA (N = 194)		**Bendamustine + Rituximab (N = 188)**	
Adverse Reaction by Body System	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Blood & lymphatic system disorders				
Neutropenia[a]	65	62	50	44
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Infections & infestations				
Upper respiratory tract infection[a]	39	2	23	2
Lower respiratory tract infection[a]	18	2	10	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	19	1	13	0

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Metabolism and nutrition disorders				
Tumor lysis syndrome	3	3	1	1
[a]Includes multiple adverse reaction terms.				

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

Blood & lymphatic system disorders: anemia (16%), thrombocytopenia (15%), febrile neutropenia (4%)

Gastrointestinal disorders: nausea (21%), constipation (14%), abdominal pain (13%), mucositis (10%), vomiting (8%)

Respiratory disorders: cough (22%)

General disorders and administration site conditions: fatigue (22%), pyrexia (15%)

Skin disorders: rash (13%)

Nervous system and psychiatric disorders: headache (11%), insomnia (11%)

Infections & infestations: pneumonia (10%), sepsis (1%)

During treatment with single agent VENCLEXTA after completion of VEN+R combination treatment, the most common all grade adverse reactions (≥10% patients) reported were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infections (11%).The most common grade 3 or 4 adverse reaction (≥2% patients) were neutropenia (12%) and anemia (3%).

Laboratory Abnormalities

Table 12 describes common treatment-emergent laboratory abnormalities identified in the MURANO trial.

Table 12. Common (≥10%) New or Worsening Laboratory Abnormalities Occurring at ≥5% (Any Grade) or ≥2% (Grade 3 or 4) Higher Incidence with VEN+R Compared with B+R

	VENCLEXTA + Rituximab N=194		**Bendamustine + Rituximab N=188**	
Laboratory Abnormality	**All Grades[a] (%)**	**Grade 3 or 4 (%)**	**All Grades[a] (%)**	**Grade 3 or 4 (%)**
Hematology				
Leukopenia	89	46	81	35
Lymphopenia	87	56	79	55
Neutropenia	86	64	84	59
Chemistry				
Hypocalcemia	62	5	51	2
Hypophosphatemia	57	14	35	4

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AST/SGOT increased	46	2	31	3
Hyperuricemia	36	36	33	33
Alkaline phosphatase increased	35	1	20	1
Hyperbilirubinemia	33	4	26	3
Hyponatremia	30	6	20	3
Hypokalemia	29	6	18	3
Hyperkalemia	24	3	19	2
Hypernatremia	24	1	13	0
Hypoglycemia	16	2	7	0
[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

New Grade 4 laboratory abnormalities reported in ≥2% of patients treated with VEN+R included neutropenia (31%), lymphopenia (16%), leukopenia (6%), thrombocytopenia (6%), hyperuricemia (4%), hypocalcemia (2%), hypoglycemia (2%), and hypermagnesemia (2%).

Monotherapy Studies (M13-982, M14-032, and M12-175)

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data from three single-arm trials (M13-982, M14-032, and M12-175). In the pooled dataset, consisting of 352 patients with previously treated CLL or SLL, the median age was 66 years (range: 28 to 85 years), 93% were white, and 68% were male. The median number of prior therapies was 3 (range: 0 to 15). The median duration of treatment with VENCLEXTA at the time of data analysis was 14.5 months (range: 0 to 50 months). Fifty-two percent of patients received VENCLEXTA for more than 60 weeks.

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 commonly (2 patients) from septic shock. Serious adverse reactions were reported in 52% of patients, with the most frequent (≥5%) being pneumonia (9%), febrile neutropenia (5%), and sepsis (5%).

Adverse reactions led to treatment discontinuation in 9% of patients, dose reduction in 13%, and dose interruption in 36%. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and autoimmune hemolytic anemia. The most frequent adverse reaction (≥5%) leading to dose reductions or interruptions was neutropenia (8%).

Adverse reactions identified in these trials of single-agent VENCLEXTA are presented in Table 13.

Table 13. Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients with Previously Treated CLL/SLL (VENCLEXTA Monotherapy)

Body System	Adverse Reaction	Any Grade (%) N=352	Grade ≥3 (%) N=352
	Neutropenia[a]	50	45

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Blood and lymphatic system disorders	Anemia[a]	33	18
	Thrombocytopenia[a]	29	20
	Lymphopenia[a]	11	7
	Febrile neutropenia	6	6
Gastrointestinal disorders	Diarrhea	43	3
	Nausea	42	1
	Abdominal pain[a]	18	3
	Vomiting	16	1
	Constipation	16	<1
	Mucositis[a]	13	<1
General disorders and administration site conditions	Fatigue[a]	32	4
	Edema[a]	22	2
	Pyrexia	18	<1
Infections and infestations	Upper respiratory tract infection[a]	36	1
	Pneumonia[a]	14	8
	Lower respiratory tract infection[a]	11	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a]	29	2
	Arthralgia	12	<1
Nervous system disorders	Headache	18	<1
	Dizziness[a]	14	0
Respiratory, thoracic, and mediastinal disorders	Cough[a]	22	0
	Dyspnea[a]	13	1
Skin and subcutaneous tissue disorders	Rash[a]	18	<1
Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0. [a]Includes multiple adverse reaction terms.			

Laboratory Abnormalities

Table 14 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline. The most common (>5%) Grade 4 laboratory abnormalities observed with VENCLEXTA monotherapy were hematologic laboratory abnormalities, including neutropenia (33%), leukopenia (11%), thrombocytopenia (15%), and lymphopenia (9%).

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Table 14. New or Worsening Laboratory Abnormalities with VENCLEXTA Monotherapy (≥40% Any Grade or ≥10% Grade 3 or 4)

Laboratory Abnormality	All Grades[a] (%) N=352	Grade 3 or 4 (%) N=352
Hematology		
Leukopenia	89	42
Neutropenia	87	63
Lymphopenia	74	40
Anemia	71	26
Thrombocytopenia	64	31
Chemistry		
Hypocalcemia	87	12
Hyperglycemia	67	7
Hyperkalemia	59	5
AST increased	53	3
Hypoalbuminemia	49	2
Hypophosphatemia	45	11
Hyponatremia	40	9

[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.

Important Adverse Reactions

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA.

CLL14

The incidence of TLS was 1% (3/212) in patients treated with VEN+G [*see Warnings and Precautions (5.1)*]. All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

MURANO

In the open-label randomized phase 3 study, the incidence of TLS was 3% (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in sections 2.1 and 2.2 *[see Dosage and Administration (2.1, 2.2)]*. All events of TLS occurred during the VENCLEXTA ramp-up period and were resolved within two days. All six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures described in sections 2.1 and 2.2 *[see Dosage and Administration (2.1, 2.2)]*. Rates of laboratory abnormalities relevant to TLS for patients treated with VEN+R are presented in Table 12.

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Monotherapy Studies (M13-982 and M14-032)

In 168 patients with CLL treated according to recommendations described in sections 2.1 and 2.2, the rate of TLS was 2% *[see Dosage and Administration (2.1, 2.2)]*. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events. The events occurred in patients who had a lymph node(s) ≥5 cm and/or ALC ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CLcr ≥50 mL/min. Laboratory abnormalities relevant to TLS were hyperkalemia (17% all Grades, 1% Grade ≥3), hyperphosphatemia (14% all Grades, 2% Grade ≥3), hypocalcemia (16% all Grades, 2% Grade ≥3), and hyperuricemia (10% all Grades, <1% Grade ≥3).

In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting doses, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. After this experience, TLS risk assessment, dosing regimen, TLS prophylaxis and monitoring measures were revised *[see Dosage and Administration (2.1, 2.2)]*.

6.2 Clinical Trial Experience with AML

The safety of VENCLEXTA (400 mg daily dose) in combination with azacitidine (n=67) or decitabine (n= 13) and VENCLEXTA (600 mg daily dose) in combination with low-dose cytarabine (n= 61) is based on two non-randomized trials of patients with newly-diagnosed AML *[see Clinical Studies (14.3)]*. The median duration of exposure for patients taking VENCLEXTA in combination with azacitidine and decitabine was 6.5 months (range: 0.1 to 31.9 months) and 8.4 months (range: 0.5 to 22.3 months), respectively. The median duration of exposure for patients taking VENCLEXTA in combination with low dose cytarabine was 3.9 months (range: 0.2 to 29.2 months).

VENCLEXTA in Combination with Azacitidine or Decitabine

Azacitidine

The most common adverse reactions (≥30%) of any grade were nausea, diarrhea, constipation, neutropenia, thrombocytopenia, hemorrhage, peripheral edema, vomiting, fatigue, febrile neutropenia, rash, and anemia.

Serious adverse reactions were reported in 75% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia (excluding fungal), sepsis (excluding fungal), respiratory failure, and multiple organ dysfunction syndrome.

The incidence of fatal adverse drug reactions was 1.5% within 30 days of starting treatment. No reaction had an incidence of ≥2%.

Discontinuations due to adverse reactions occurred in 21% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were febrile neutropenia and pneumonia (excluding fungal).

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Dosage interruptions due to adverse reactions occurred in 61% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were neutropenia, febrile neutropenia, and pneumonia (excluding fungal).

Dosage reductions due to adverse reactions occurred in 12% of patients. The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia.

Decitabine

The most common adverse reactions (≥30%) of any grade were febrile neutropenia, constipation, fatigue, thrombocytopenia, abdominal pain, dizziness, hemorrhage, nausea, pneumonia (excluding fungal), sepsis (excluding fungal), cough, diarrhea, neutropenia, back pain, hypotension, myalgia, oropharyngeal pain, peripheral edema, pyrexia, and rash.

Serious adverse reactions were reported in 85% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, cellulitis, and localized infection.

One (8%) fatal adverse drug reaction of bacteremia occurred within 30 days of starting treatment.

Discontinuations due to adverse reactions occurred in 38% of patients. The most frequent adverse reaction leading to drug discontinuation (≥5%) was pneumonia (excluding fungal).

Dosage interruptions due to adverse reactions occurred in 62% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were febrile neutropenia, neutropenia, and pneumonia (excluding fungal).

Dosage reductions due to adverse reactions occurred in 15% of patients. The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia.

Adverse reactions reported in patients with newly-diagnosed AML using VENCLEXTA in combination with azacitidine or decitabine are presented in Table 15.

Table 15. Adverse Reactions Reported in ≥30% (Any Grade) or ≥5% (Grade ≥3) of Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Body System	Adverse Reaction	VENCLEXTA in Combination with Azacitidine		VENCLEXTA in Combination with Decitabine	
		Any Grade (%) N = 67	Grade ≥3 (%) N = 67	Any Grade (%) N = 13	Grade ≥3 (%) N = 13
Blood and lymphatic system disorders	Thrombocytopenia[a]	49	45	54	54
	Neutropenia[a]	49	49	38	38
	Febrile neutropenia	36	36	69	69
	Anemia[a]	30	30	15	15
Gastrointestinal disorders	Nausea	58	1	46	0
	Diarrhea	54	3	38	8

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	Constipation	49	3	62	0
	Vomiting[a]	40	0	23	0
	Abdominal pain[a]	22	4	46	0
General disorders and administration site conditions	Peripheral edema[a]	46	1	31	0
	Fatigue[a]	36	7	62	15
	Pyrexia	21	3	31	0
	Cachexia	0	0	8	8
	Multiple organ dysfunction syndrome	6	6	0	0
Infections and infestations	Pneumonia (excluding fungal)[a]	27	25	46	31
	Sepsis (excluding fungal)[a]	13	13	46	46
	Urinary tract infection	16	6	23	0
	Cellulitis	6	0	15	8
	Localized infection	0	0	8	8
Musculoskeletal and connective tissue disorders	Back pain	15	0	31	0
	Myalgia[a]	10	0	31	0
Nervous system disorders	Dizziness[a]	28	1	46	0
Skin and subcutaneous tissue disorders	Rash[a]	33	1	31	0
Respiratory, thoracic and mediastinal disorders	Cough[a]	25	0	38	0
	Hypoxia	18	6	15	0
	Oropharyngeal pain	9	0	31	0
Vascular disorders	Hemorrhage[a]	46	7	46	0
	Hypotension[a]	21	6	31	0
	Hypertension	12	7	15	8

Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Includes multiple adverse reaction terms.

Laboratory Abnormalities

Table 16 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

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Table 16. New or Worsening Laboratory Abnormalities with VENCLEXTA Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Laboratory Abnormality	VENCLEXTA in Combination with Azacitidine		VENCLEXTA in Combination with Decitabine	
	Any Grade[a] (%) N = 67	Grade 3 or 4[a] (%) N = 67	Any Grade[a] (%) N = 13	Grade 3 or 4[a] (%) N = 13
Hematology				
Neutropenia	100	100	100	100
Leukopenia	100	98	100	100
Thrombocytopenia	91	78	83	83
Lymphopenia	88	73	100	92
Anemia	57	57	69	69
Chemistry				
Hyperglycemia	75	12	69	0
Hypocalcemia	58	7	85	0
Hypoalbuminemia	52	4	38	8
Hypokalemia	49	7	46	0
Hyponatremia	49	4	38	0
Hypophosphatemia	46	15	23	8
Hyperbilirubinemia	45	9	46	15
Hypomagnesemia	21	0	54	8

[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.

VENCLEXTA in Combination with Low-Dose Cytarabine

The most common adverse reactions (≥30%) of any grade were nausea, thrombocytopenia, hemorrhage, febrile neutropenia, neutropenia, diarrhea, fatigue, constipation, and dyspnea.

Serious adverse reactions were reported in 95% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, sepsis (excluding fungal), hemorrhage, pneumonia (excluding fungal), and device-related infection.

The incidence of fatal adverse drug reactions was 4.9% within 30 days of starting treatment with no reaction having an incidence of ≥2%.

Discontinuations due to adverse reactions occurred in 33% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were hemorrhage and sepsis (excluding fungal).

Dosage interruptions due to adverse reactions occurred in 52% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were thrombocytopenia, neutropenia, and febrile neutropenia.

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Dosage reductions due to adverse reactions occurred in 8% of patients. The most frequent adverse reaction leading to dose reduction (≥2%) was thrombocytopenia.

Adverse reactions reported in patients with newly-diagnosed AML receiving VENCLEXTA in combination with low-dose cytarabine are presented in Table 17.

Table 17. Adverse Reactions Reported in ≥30% (Any Grade) or ≥5% (Grade ≥3) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Body System	Adverse Reaction	Any Grade (%) N = 61	Grade ≥3 (%) N = 61
Blood and lymphatic system disorders	Thrombocytopenia[a]	59	59
	Neutropenia[a]	46	46
	Febrile neutropenia	46	44
	Anemia[a]	26	26
Gastrointestinal disorders	Nausea	64	2
	Diarrhea	44	3
	Constipation	33	0
General disorders and administration site conditions	Fatigue[a]	44	10
Infections and infestations	Sepsis[a]	20	18
	Pneumonia[a]	18	16
	Device related infection	13	11
	Urinary tract infection	8	7
Metabolic and nutritional disorders	Decreased appetite[a]	28	7
Respiratory disorders	Dyspnea[a]	31	3
Vascular disorders	Hemorrhage[a]	49	15
	Hypotension[a]	21	7
	Hypertension	15	8

Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Includes multiple adverse reaction terms.

Laboratory Abnormalities

Table 18 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

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Table 18. New or Worsening Laboratory Abnormalities with VENCLEXTA Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Laboratory Abnormality	All Grades[a] (%) N = 61	Grade 3 or 4[a] (%) N = 61
Hematology		
Thrombocytopenia	100	96
Neutropenia	96	96
Leukopenia	96	96
Lymphopenia	93	66
Anemia	61	59
Chemistry		
Hyperglycemia	85	8
Hypocalcemia	79	16
Hyponatremia	62	11
Hyperbilirubinemia	57	3
Hypoalbuminemia	59	5
Hypokalemia	56	20
Hypophosphatemia	51	21
Hypomagnesemia	46	0
Blood creatinine increased	46	3
Blood bicarbonate decreased	41	0

[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.

Tumor Lysis Syndrome

Tumor lysis syndrome is an important risk when initiating treatment in patients with AML. The incidence of TLS was 3% (2/61) with VENCLEXTA in combination with low-dose cytarabine with implementation of dose ramp-up schedule in addition to standard prophylaxis and monitoring measures. All events were laboratory TLS, and all patients were able to reach the target dose.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VENCLEXTA

Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may increase VENCLEXTA toxicities, including the risk of TLS *[see Warnings and Precautions (5)]*.

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Concomitant use with a strong CYP3A inhibitor at initiation and during the ramp-up phase in patients with CLL/SLL is contraindicated *[see Contraindications (4)]*.

In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.3, 2.4)]*.

In patients with AML, adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.3, 2.4)]*.

Resume the VENCLEXTA dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.3, 2.4)]*.

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

Strong or Moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases venetoclax C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers.

7.2 Effect of VENCLEXTA on Other Drugs

Warfarin

Concomitant use of VENCLEXTA increases warfarin C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may increase the risk of bleeding. Closely monitor international normalized ratio (INR) in patients using warfarin concomitantly with VENCLEXTA.

P-gp Substrates

Concomitant use of VENCLEXTA increases C_{max} and AUC_{inf} of P-gp substrates *[see Clinical Pharmacology (12.3)]*, which may increase toxicities of these substrates. Avoid concomitant use of VENCLEXTA with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on VENCLEXTA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Based on toxicity observed in mice, VENCLEXTA may cause fetal harm when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on AUC at a human dose of 400 mg daily. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential risk to a fetus.

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The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal data

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the period of organogenesis. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at a dose of 400 mg daily). No teratogenicity was observed in either the mouse or the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of VENCLEXTA in human milk, the effects of VENCLEXTA on the breastfed child, or the effects of VENCLEXTA on milk production. Venetoclax was present in the milk when administered to lactating rats *(see Data)*.

Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from VENCLEXTA is unknown, advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

Data

Animal Data

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8 to 10 days parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites.

8.3 Females and Males of Reproductive Potential

VENCLEXTA may cause fetal harm *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential before initiation of VENCLEXTA *[see Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose *[see Use in Specific Populations (8.1)]*.

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Infertility

Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

In a juvenile toxicology study, mice were administered venetoclax at 10, 30, or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor, and hunched posture at ≥30 mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at ≥10 mg/kg/day; a dose of 10 mg/kg/day is approximately 0.06 times the clinical dose of 400 mg on a mg/m^2 basis for a 20 kg child.

8.5 Geriatric Use

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Of the 352 patients with previously treated CLL/SLL evaluated for safety from 3 open-label trials of VENCLEXTA monotherapy, 57% (201/352) were ≥65 years of age and 18% (62/352) were ≥75 years of age.

No clinically meaningful differences in safety and effectiveness were observed between older and younger patients in the combination and monotherapy studies.

Acute Myeloid Leukemia

Of the 67 patients treated with VENCLEXTA in combination with azacitidine in the clinical trial, 96% were ≥65 years of age and 50% were ≥ 75 years of age. Of the 13 patients treated with VENCLEXTA in combination with decitabine in the clinical trial, 100% were ≥65 years of age and 26% were ≥ 75 years of age. Of the 61 patients treated with VENCLEXTA in combination with low-dose cytarabine, 97% were ≥65 years of age and 66% were ≥75 years of age.

The efficacy and safety data presented in the Adverse Reactions and Clinical Studies sections were obtained from these patients *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*. There are insufficient patient numbers to show differences in safety and effectiveness between geriatric and younger patients.

8.6 Renal Impairment

Due to the increased risk of TLS, patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.1)]*.

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr ≥ 30 mL/min *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with severe renal impairment (CLcr < 30 mL/min) or patients on dialysis.

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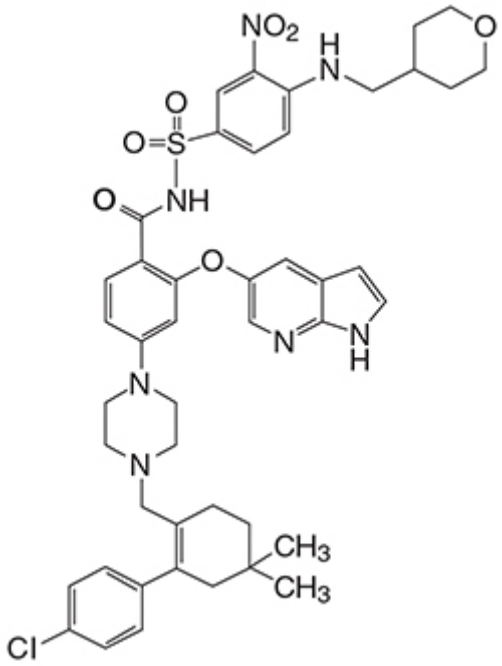
10 OVERDOSAGE

There is no specific antidote for VENCLEXTA. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt VENCLEXTA and monitor carefully for signs and symptoms of TLS along with other toxicities *[see Dosage and Administration (2.2, 2.3)]*. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

11 DESCRIPTION

Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. Venetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) and has the following chemical structure:



VENCLEXTA tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol and titanium dioxide. Each tablet is debossed with “V” on one side and “10”, “50” or “100” corresponding to the tablet strength on the other side.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL and AML cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

12.2 Pharmacodynamics

Based on the exposure response analyses for efficacy, a relationship between drug exposure and a greater likelihood of response was observed in clinical studies in patients with CLL/SLL, and in patients with AML. Based on the exposure response analyses for safety, a relationship between drug exposure and a greater likelihood of some safety events was observed in clinical studies in patients with AML. No exposure-safety relationship was observed in patients with CLL/SLL at doses up to 1200 mg given as monotherapy and up to 600 mg given in combination with rituximab.

Cardiac Electrophysiology

The effect of multiple doses of VENCLEXTA up to 1200 mg once daily (2 times the maximum approved recommended dosage) on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated hematologic malignancies. VENCLEXTA had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

12.3 Pharmacokinetics

Venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 mcg/mL and AUC_{0-24} was 32.8 ± 16.9 mcg•h/mL following administration of 400 mg once daily with a low-fat meal. Venetoclax steady state AUC increased proportionally over the dose range of 150 to 800 mg (0.25 to 1.33 times the maximum approved recommended dosage). The pharmacokinetics of venetoclax does not change over time.

Absorption

Maximum plasma concentration of venetoclax was reached 5 to 8 hours following multiple oral administration under fed conditions.

Effect of Food

Administration with a low-fat meal (approximately 512 kilocalories, 25% fat calories, 60% carbohydrate calories, and 15% protein calories) increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal (approximately 753 kilocalories, 55% fat calories, 28% carbohydrate calories, and 17% protein calories) increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions.

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Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 micromolar (0.87-26 mcg/mL). The mean blood-to-plasma ratio was 0.57. The apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256-321 L in patients.

Elimination

The terminal elimination half-life of venetoclax was approximately 26 hours.

Metabolism

Venetoclax is predominantly metabolized by CYP3A *in vitro*. The major metabolite identified in plasma, M27, has an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro* and its AUC represented 80% of the parent AUC.

Excretion

After single oral dose of radiolabeled [^{14}C]-venetoclax 200 mg to healthy subjects, > 99.9% of the dose was recovered in feces (20.8% as unchanged) and < 0.1% in urine within 9 days.

Specific Populations

No clinically significant differences in the pharmacokinetics of venetoclax were observed based on age (19 to 90 years), sex, race (White, Black, Asians, and Others), weight, mild to moderate renal impairment (CLcr 30 to 89 mL/min, calculated by Cockcroft-Gault), or mild to moderate hepatic impairment (normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin 1 to 3 times ULN). The effect of severe renal impairment (CLcr < 30 mL/min), dialysis, or severe hepatic impairment (total bilirubin > 3 times ULN) on venetoclax pharmacokinetics is unknown.

Drug Interactions Studies

Clinical Studies

No clinically significant differences in venetoclax pharmacokinetics were observed when co-administered with azacitidine, azithromycin, cytarabine, decitabine, gastric acid reducing agents, obinutuzumab, or rituximab.

Ketoconazole

Concomitant use of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) 400 mg once daily for 7 days increased venetoclax C_{max} by 130% and AUC_{inf} by 540% *[see Drug Interactions (7.1)]*.

Ritonavir

Concomitant use of ritonavir (a strong CYP3A, P-gp and OATP1B1/B3 inhibitor) 50 mg once daily for 14 days increased venetoclax C_{max} by 140% and AUC by 690% *[see Drug Interactions (7.1)]*.

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Posaconazole

Concomitant use of posaconazole (a strong CYP3A and P-gp inhibitor) 300 mg with venetoclax 50 mg and 100 mg for 7 days resulted in 61% and 86% higher venetoclax C_{max}, respectively, compared with venetoclax 400 mg administered alone. The venetoclax AUC_{24} was 90% and 144% higher, respectively.

Rifampin

Concomitant use of a single dose of rifampin (an OATP1B1/1B3 and P-gp inhibitor) 600 mg increased venetoclax C_{max} by 106% and AUC_{inf} by 78%. Concomitant use of multiple doses of rifampin (as a strong CYP3A inducer) 600 mg once daily for 13 days decreased venetoclax C_{max} by 42% and AUC_{inf} by 71% *[see Drug Interactions (7.1)]*.

Warfarin

Concomitant use of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

Digoxin

Concomitant use of a single dose of venetoclax 100 mg with digoxin (a P-gp substrate) 0.5 mg increased digoxin C_{max} by 35% and AUC_{inf} by 9% *[see Drug Interactions (7.2)]*.

In Vitro Studies

Venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1.

Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Venetoclax is an inhibitor and substrate of P-gp and BCRP and weak inhibitor of OATP1B1.

Venetoclax is not an inhibitor of OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with venetoclax.

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at doses up to 835 mg/kg. The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluate mating, fertilization, and embryonic development through implantation. There were no effects of venetoclax on estrous cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day. However, a risk to human

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male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at exposures as low as 0.5 times the human AUC exposure at a dose of 400 mg.

13.2 Animal Toxicology and/or Pharmacology

In dogs, venetoclax caused single-cell necrosis in various tissues, including the gallbladder, exocrine pancreas, and stomach with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

In addition, after approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Combination Therapy

CLL14

CLL14 (BO25323) was a randomized (1:1), multicenter, open label, actively controlled, phase 3 trial (NCT02242942) that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or CLcr < 70 mL/min). The trial required hepatic transaminases and total bilirubin ≤2 times upper limit of normal and excluded patients with Richter's transformation or any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system.

All patients received obinutuzumab at 1000 mg on Day 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2), and on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. Patients in the VEN+G arm began the 5-week VENCLEXTA ramp-up schedule *[see Dosage and Administration (2.1, 2.2)]* on Day 22 of Cycle 1, and received VENCLEXTA 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomized to the GClb arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1 to 12. Each cycle was 28 days.

A total of 432 patients were randomized, 216 to each study arm. Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, 67% were male; 36% and 43% were Binet stage B and C, respectively, and 88% had ECOG performance status <2. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLcr <70 mL/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 7%, 11q deletion in 19%, and unmutated *IgVH* in 57%.

The major efficacy outcome was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median duration of follow-up for PFS was 28 months (range: 0.1 to 36 months).

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Efficacy results for CLL14 are shown in Table 19. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 19: Efficacy Results in CLL14

Endpoint	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Progression-free survival[a]		
Number of events, n (%)	29 (13)	79 (37)
Disease progression	14 (6)	71 (33)
Death	15 (7)	8 (4)
Median, months	Not Reached	Not Reached
HR (95% CI)[b]	0.33 (0.22, 0.51)	
p-value[b]	< 0.0001	
Response rate[c], n (%)		
ORR[d]	183 (85)	154 (71)
95% CI	(79, 89)	(65, 77)
CR	100 (46)	47 (22)
CR+CRi[d]	107 (50)	50 (23)
PR	76 (35)	104 (48)

CI = confidence interval; HR = hazard ratio; CR = complete remission; CRi = complete remission with incomplete marrow recovery; PR = partial remission; ORR = overall response rate (CR + CRi + PR).
[a]From randomization until earliest event of disease progression or death due to any cause. IRC-assessed; Kaplan-Meier estimate.
[b]HR estimate is based on Cox-proportional hazards model stratified by Binet Stage and geographic region; p-value based on log rank test stratified by the same factors.
[c]Per 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines.
[d]p-values based on Cochran-Mantel-Haenszel test; p=0.0007 for ORR; p <0.0001 for CR+CRi.

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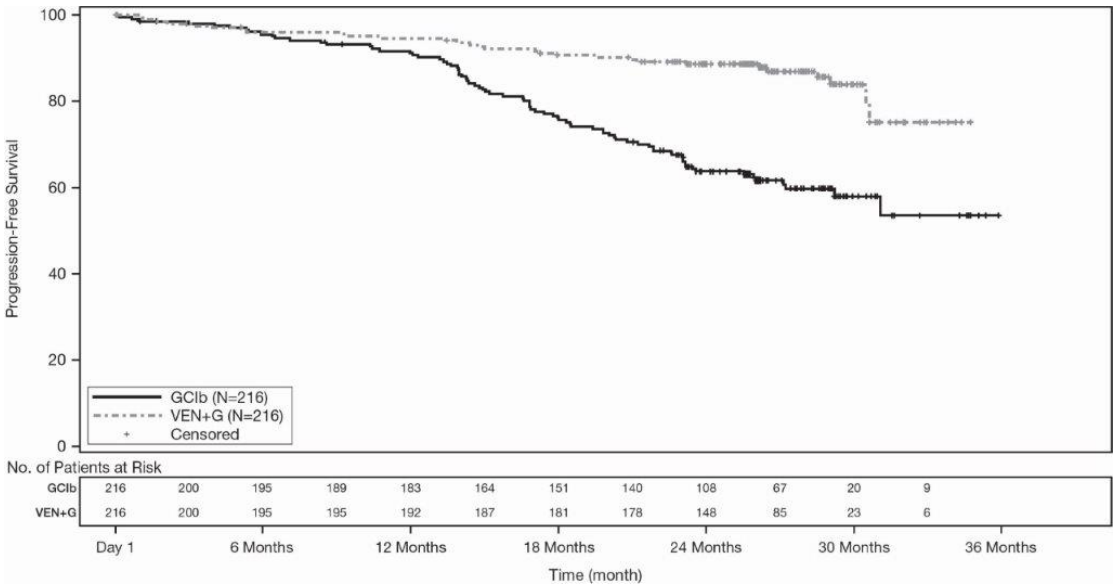
Figure 1: Kaplan-Meier Curve of IRC-Assessed Progression-free Survival in CLL14



At the time of analysis, median overall survival (OS) had not been reached, with fewer than 10% of patients experiencing an event. The median duration of follow-up for OS was 28 months.

Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The definition of negative status was less than one CLL cell per 10^4 leukocytes. Rates of MRD negativity 3 months after the completion of treatment regardless of response and in patients who achieved CR are shown in Table 20. At this assessment, 134 patients in the VEN+G arm who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 122 patients (91%) were MRD negative in both peripheral blood and bone marrow.

Table 20: Minimal Residual Disease Negativity Rates Three Months After the Completion of Treatment in CLL14

	VENCLEXTA + Obinutuzumab	**Obinutuzumab + Chlorambucil**
MRD negativity rate (ITT population)		
N	216	216
Bone marrow, n (%)	123 (57)	37 (17)
95% CI	(50, 64)	(12, 23)
p-value[a]	<0.0001	
Peripheral blood, n (%)	163 (76)	76 (35)
95% CI	(69, 81)	(29, 42)
p-value[a]	<0.0001	
MRD negativity rate in patients with CR		
N	100	47
Bone marrow, n (%)	69 (69)	21 (45)

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95% CI	(59, 78)	(30, 60)
p-value[a]	0.0048	
Peripheral blood, n (%)	87 (87)	29 (62)
95% CI	(79, 93)	(46, 75)
p-value[a]	0.0005	
CI = confidence interval; CR = complete remission. [a]p-value based on Chi-square test		

Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 58% (126/216) in patients treated with VEN+G and 9% (20/216) in patients treated with GClb.

MURANO

MURANO was a randomized (1:1), multicenter, open label study (NCT02005471) that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab (VEN+R) versus bendamustine in combination with rituximab (B+R) in patients with CLL who had received at least one line of prior therapy. Patients in the VEN+R arm completed the 5-week ramp-up schedule *[see Dosage and Administration (2.1, 2.2)]* and received VENCLEXTA 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated intravenously after the 5-week dose ramp-up at 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2-6. Each cycle was 28 days. Patients randomized to B+R received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles (28-day cycle) and rituximab at the above described dose and schedule.

A total of 389 patients were randomized: 194 to the VEN+R arm and 195 to the B+R arm. Baseline demographic and disease characteristics were similar between the VEN+R and B+R arms. The median age was 65 years (range: 22-85 years), 97% were white, 74% were male, and 99% had ECOG performance status <2. Median prior lines of therapy was 1 (range: 1-5); 59% had received 1 prior therapy, 26% had received 2 prior therapies, and 16% had received 3 or more prior therapies. Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, *TP53* mutations in 25%, 11q deletion in 32%, and unmutated *IgVH* in 63%.

Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median follow-up for PFS was 23.4 months (range: 0 to 37.4+ months).

Efficacy results for MURANO are shown in Table 21. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 21. IRC-Assessed Efficacy Results in MURANO

Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Progression-free survival[a]		
Number of events, n (%)	35 (18)	106 (54)

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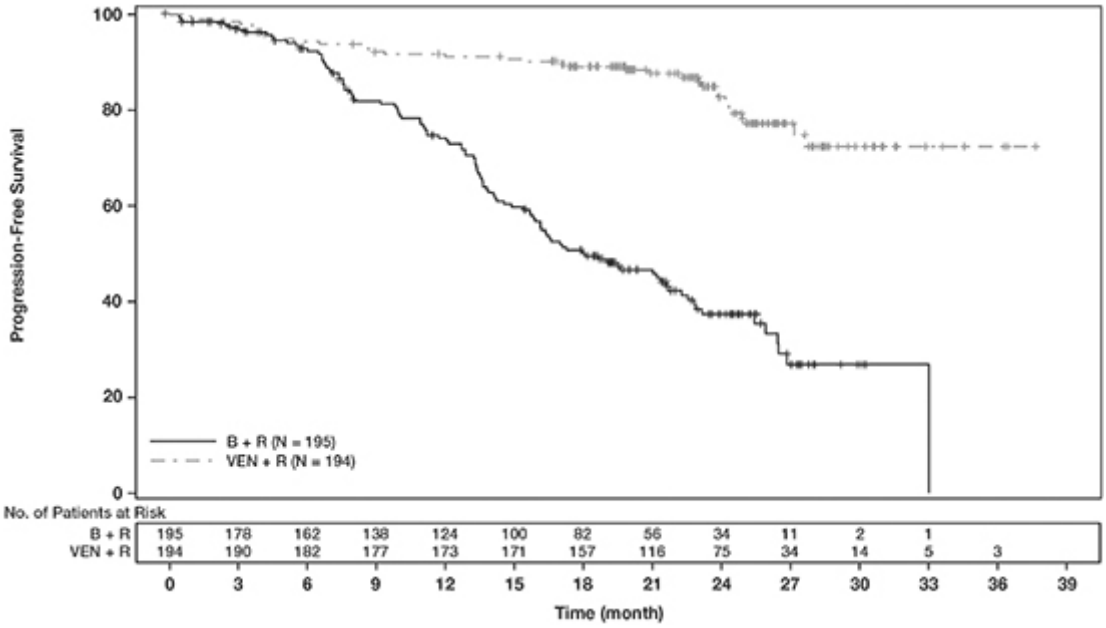
Disease progression, n	26	91
Death events, n	9	15
Median, months (95% CI)	Not Reached	18.1 (15.8, 22.3)
HR (95% CI)[b]	0.19 (0.13, 0.28)	
p-value[b]	<0.0001	
Response rate[c], n (%)		
ORR	179 (92)	141 (72)
95% CI	(88, 96)	(65, 78)
CR+CRi	16 (8)	7 (4)
nPR	3 (2)	1 (1)
PR	160 (82)	133 (68)

CI = confidence interval; HR = hazard ratio; CR = complete remission; CRi = complete remission with incomplete marrow recovery; nPR = nodular partial remission; PR = partial remission; ORR = overall response rate (CR + CRi + nPR + PR).
[a]Kaplan-Meier estimate.
[b]HR estimate is based on Cox-proportional hazards model stratified by 17p deletion, risk status, and geographic region; p-value based on log-rank test stratified by the same factors.
[c]Per 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines.

Figure 2. Kaplan-Meier Curve of IRC-Assessed Progression-free Survival in MURANO



At the time of analysis, median overall survival had not been reached in either arm after a median follow-up of 22.9 months.

At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood in patients who achieved PR or better was 53% (103/194) in the VEN+R arm and 12% (23/195) in

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the B+R arm. The MRD-negative CR/CRi rate at this timepoint was 3% (6/194) in the VEN+R arm and 2% (3/195) in the B+R arm.

Monotherapy

The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies.

Study M13-982

The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. Patients received VENCLEXTA via a weekly ramp-up schedule starting at 20 mg and ramping to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity.

Efficacy was based on overall response rate (ORR) as assessed by an Independent Review Committee (IRC).

Table 22 summarizes the baseline demographic and disease characteristics of the study population.

Table 22. Baseline Patient Characteristics in Study M13-982

Characteristic	N = 106
Age, years; median (range)	67 (37-83)
White; %	97
Male; %	65
ECOG performance status; %	
0	40
1	52
2	8
Tumor burden; %	
Absolute lymphocyte count ≥25 x 10^9/L	50
One or more nodes ≥5 cm	53
Number of prior therapies; median (range)	2.5 (1-10)
Time since diagnosis, years; median (range)[a]	6.6 (0.1-32.1)
[a]N=105.	

The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months). Efficacy results are shown in Table 23.

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Table 23. Efficacy Results per IRC for Patients with Previously Treated CLL with 17p Deletion in Study M13-982

Endpoint	VENCLEXTA N=106
ORR, n (%)[a] (95% CI)	85 (80) (71, 87)
CR + CRi, n (%)	8 (8)
CR, n (%)	6 (6)
CRi, n (%)	2 (2)
nPR, n (%)	3 (3)
PR, n (%)	74 (70)

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.
[a]Per 2008 IWCLL guidelines.

The median time to first response was 0.8 months (range: 0.1 to 8.1 months).

Based on a later data cutoff date and investigator-assessed efficacy, the duration of response (DOR) ranged from 2.9 to 32.8+ months. The median DOR has not been reached with median follow-up of 22 months.

MRD was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with VENCLEXTA. Three percent (3/106) achieved MRD negativity in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes).

Study M12-175

Study M12-175 (NCT01328626) was a multicenter, open-label trial that enrolled previously treated patients with CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (59 with CLL, 8 with SLL) who had received a 400 mg daily dose of VENCLEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months).

The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had ALC ≥25 x 10^9/L, 33% had documented unmutated *IgVH*, and 21% had documented 17p deletion.

Efficacy in CLL was evaluated according to 2008 IWCLL guidelines. As assessed by an IRC, the ORR was 71% (95% CI: 58%, 82%), CR + CRi rate was 7%, and PR rate was 64%.

Based on investigator assessments, the ORR in patients with CLL was 80% (14% CR+ CRi, 66% PR + nPR). With an estimated median follow-up of 25.2 months, the DOR ranged from 2.3+ to 48.6+ months. Of the 47 responders, 83% had a DOR of at least 12 months.

For the 8 patients with SLL, the investigator-assessed ORR was 100%.

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Study M14-032

Study M14-032 (NCT02141282) was an open-label, multicenter, study that evaluated the efficacy of VENCLEXTA in patients with CLL who had been previously treated with and progressed on or after ibrutinib or idelalisib. Patients received a daily dose of 400 mg of VENCLEXTA following the ramp-up schedule. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity. At the time of analysis, the median duration of treatment was 14.3 months (range: 0.1 to 31.4 months).

Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥5 cm, 31% had an absolute lymphocyte count ≥25 x 10^9/L, 57% had documented unmutated *IgVH*, and 39% had documented 17p deletion.

Efficacy was based on 2008 IWCLL guidelines. Based on IRC assessment, the ORR was 70% (95% CI: 61%, 78%), with a CR + CRi rate of 1%, and PR rate of 69%.

Based on investigator assessment, the ORR was 65% (95% CI: 56%, 74%). The median DOR per investigator has not been reached with an estimated median follow-up of 14.6 months.

14.2 Acute Myeloid Leukemia

VENCLEXTA was studied in two open-label non-randomized trials in patients with newly-diagnosed AML who were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr <45 mL/min or other comorbidity. Efficacy was established based on the rate of complete remission (CR) and the duration of CR.

Study M14-358

VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA via a daily ramp-up to a final 400 mg once daily dose *[see Dosage and Administration (2.1)]*. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Decitabine at 20 mg/m^2 was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity, see azacitidine full prescribing information. Dose reductions for decitabine were not implemented in the clinical trial.

Table 24 summarizes the baseline demographic and disease characteristics of the study population.

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Table 24. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Characteristic	VENCLEXTA in Combination with Azacitidine N = 67	VENCLEXTA in Combination with Decitabine N = 13
Age, years; median (range)	76 (61-90)	75 (68-86)
Race		
White; %	87	77
Black or African American; %	4.5	0
Asian; %	1.5	0
Native Hawaiian or Pacific Islander; %	1.5	15
American Indian/Alaskan Native; %	0	7.7
Unreported/Other; %	6.0	0
Male; %	60	38
ECOG performance status; %		
0-1	64	92
2	33	8
3	3	0
Disease history; %		
De Novo AML	73	85
Secondary AML	27	15
Mutation analyses detected[a]; %		
TP53	21	31
IDH1 or IDH2	27	0
FLT-3	16	23
NPM1	19	15
Cytogenetic risk detected[b,c]; %		
Intermediate	64	38
Poor	34	62
Baseline comorbidities[d], %		
Severe cardiac disease	4.5	7.7
Severe pulmonary disease	1.5	0
Moderate hepatic impairment	9	0
Creatinine clearance <45 mL/min	13	7.7

[a]Includes 6 patients with insufficient sample for analysis in the azacitidine group and 4 in the decitabine group.
[b]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014.
[c]No mitosis in 1 patient in azacitidine group (excluded favorable risk by Fluorescence in situ Hybridization [FISH] analysis).
[d]Patients may have had more than one comorbidity.

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The efficacy results are shown in Table 25.

Table 25. Efficacy Results for Patients with Newly-Diagnosed AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Efficacy Outcomes	VENCLEXTA in Combination with Azacitidine N = 67	VENCLEXTA in Combination with Decitabine N = 13
CR, n (%) (95% CI)	25 (37) (26, 50)	7 (54) (25, 81)
CRh, n (%) (95% CI)	16 (24) (14, 36)	1 (7.7) (0.2, 36)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

The median follow-up was 7.9 months (range: 0.4 to 36 months) for VENCLEXTA in combination with azacitidine. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 5.5 months (range: 0.4 to 30 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

The median follow-up was 11 months (range: 0.7 to 21 months) for VENCLEXTA in combination with decitabine. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 4.7 months (range: 1.0 to 18 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with azacitidine was 1.0 month (range: 0.7 to 8.9 months).

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with decitabine was 1.9 months (range: 0.8 to 4.2 months).

Of patients treated with VENCLEXTA in combination with azacitidine, 7.5% (5/67) subsequently received stem cell transplant.

The study enrolled 35 additional patients (age range: 65 to 74 years) who did not have known comorbidities that preclude the use of intensive induction chemotherapy and were treated with VENCLEXTA in combination with azacitidine (N=17) or decitabine (N=18).

For the 17 patients treated with VENCLEXTA in combination with azacitidine, the CR rate was 35% (95% CI: 14%, 62%). The CRh rate was 41% (95% CI: 18%, 67%). Seven (41%) patients subsequently received stem cell transplant.

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For the 18 patients treated with VENCLEXTA in combination with decitabine, the CR rate was 56% (95% CI: 31%, 79%). The CRh rate was 22% (95% CI: 6.4%, 48%). Three (17%) patients subsequently received stem cell transplant.

Study M14-387

VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02287233) of VENCLEXTA in combination with low dose cytarabine (N=82) in patients with newly-diagnosed AML, including patients with previous exposure to a hypomethylating agent for an antecedent hematologic disorder. Of those patients, 61 were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the criterion: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr ≥30 to <45 mL/min or other comorbidity.

Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose *[see Dosage and Administration (2.1)]*. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m^2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

Table 26 summarizes the baseline demographic and disease characteristics of the study population.

Table 26. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 61
Age, years; median (range)	76 (63-90)
Race	
White; %	92
Black or African American; %	1.6
Asian; %	1.6
Unreported; %	4.9
Male; %	74
ECOG performance status; %	
0-1	66
2	33
3	1.6
Disease history, %	
De novo AML	54
Secondary AML	46
Mutation analyses detected[a]; %	
TP53	8

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IDH1 or IDH2	23
FLT-3	21
NPM1	9.8
Cytogenetic risk detected[b]; %	
Intermediate	59
Poor	34
No mitoses	6.6
Baseline comorbidities[c], %	
Severe cardiac disease	9.8
Moderate hepatic impairment	4.9
Creatinine clearance ≥30 or <45 mL/min	3.3

[a]Includes 7 patients with insufficient sample for analysis.
[b]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014
[c]Patients may have had more than one comorbidity.

Efficacy results are shown in Table 27.

Table 27. Efficacy Results for Patients with Newly-Diagnosed AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Efficacy Outcomes	VENCLEXTA in Combination with Low-Dose Cytarabine N = 61
CR, n (%) (95% CI)	13 (21) (12, 34)
CRh, n (%) (95% CI)	13 (21) (12, 34)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

The median follow-up was 6.5 months (range: 0.3 to 34 months). At the time of analysis, for patients who achieved a CR, the median observed time in remission was 6.0 months (range: 0.03 to 25 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with low-dose cytarabine was 1.0 month (range: 0.8 to 9.4 months).

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The study enrolled 21 additional patients (age range: 67 to 74 years) who did not have known comorbidities that preclude the use of intensive induction chemotherapy and were treated with VENCLEXTA in combination with low-dose cytarabine. The CR rate was 33% (95% CI:15%, 57%). The CRh rate was 24% (95% CI: 8.2%, 47%). One patient (4.8%) subsequently received stem cell transplant.

16 HOW SUPPLIED/STORAGE AND HANDLING

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
CLL/SLL Starting Pack	Each pack contains four weekly wallet blister packs: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets)	0074-0579-28
Wallet containing 10 mg tablets	14 x 10 mg tablets	0074-0561-14
Wallet containing 50 mg tablets	7 x 50 mg tablets	0074-0566-07
Unit dose blister containing 10 mg tablets	2 x 10 mg tablets	0074-0561-11
Unit dose blister containing 50 mg tablet	1 x 50 mg tablet	0074-0566-11
Unit dose blister containing 100 mg tablet	1 x 100 mg tablet	0074-0576-11
Bottle containing 100 mg tablets	120 x 100 mg tablets	0074-0576-22
Bottle containing 100 mg tablets	180 x 100 mg tablets	0074-0576-34

VENCLEXTA 10 mg film-coated tablets are round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.

VENCLEXTA 50 mg film-coated tablets are oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.

VENCLEXTA 100 mg film-coated tablets are oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

Store at or below 86°F (30°C).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Tumor Lysis Syndrome**
  Advise patients of the potential risk of TLS, particularly at treatment initiation and during

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ramp-up phase, and to immediately report any signs and symptoms associated with this event (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their health care provider (HCP) for evaluation *[see Warnings and Precautions (5.1)]*.

Advise patients to be adequately hydrated every day when taking VENCLEXTA to reduce the risk of TLS. The recommended volume is 6 to 8 glasses (approximately 56 ounces total) of water each day. Patients should drink water starting 2 days before and on the day of the first dose, and every time the dose is increased *[see Dosage and Administration (2.2)]*.

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Dosage and Administration (2.2)]*.

Advise patients that it may be necessary to take VENCLEXTA in the hospital or medical office setting to allow monitoring for TLS.

- **Neutropenia**
  Advise patients to contact their HCP immediately if they develop a fever or any signs of infection. Advise patients of the need for periodic monitoring of blood counts *[see Warnings and Precautions (5.2)]*.

- **Infections**
  Advise patients to contact their HCP immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.3)]*.

- **Drug Interactions**
  Advise patients to avoid consuming grapefruit products, Seville oranges, or starfruit during treatment with VENCLEXTA. Advise patients that VENCLEXTA may interact with some drugs; therefore, advise patients to inform their health care provider of the use of any prescription medication, over-the-counter drugs, vitamins and herbal products *[see Contraindications (4) and Drug Interactions (7.1)]*.

- **Immunizations**
  Advise patients to avoid vaccination with live vaccines because they may not be safe or effective during treatment with VENCLEXTA *[see Warnings and Precautions (5.4)]*.

- **Pregnancy and Lactation**
  Advise women of the potential risk to the fetus and to avoid pregnancy during treatment with VENCLEXTA. Advise female patients of reproductive potential to use effective contraception during therapy and for at least 30 days after completing of therapy. Advise females to contact their HCP if they become pregnant, or if pregnancy is suspected, during treatment with VENCLEXTA. Also advise patients not to breastfeed while taking VENCLEXTA *[see Warnings and Precautions (5.5), and Use in Specific Populations (8.1, 8.2, and 8.3)]*.

- **Male Infertility**
  Advise patients of the possibility of infertility and possible use of sperm banking for males of reproductive potential *[see Use in Specific Populations (8.3)]*.

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Instructions for Taking VENCLEXTA

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 HCP. Advise patients to 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 *[see Dosage and Administration (2.1)]*.

Advise patients with CLL/SLL to keep VENCLEXTA in the original packaging during the first 4 weeks of treatment, and not to transfer the tablets to a different container.

Advise patients that if a dose of VENCLEXTA is missed by less than 8 hours, to take the missed dose right away and take the next dose as usual. If a dose of VENCLEXTA is missed by more than 8 hours, advise patients to wait and take the next dose at the usual time *[see Dosage and Administration (2.5)]*.

Advise patients not to take any additional dose that day if they vomit after taking VENCLEXTA, and to take the next dose at the usual time the following day.

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North Chicago, IL 60064

and

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MEDICATION GUIDE
VENCLEXTA® (ven-KLEKS-tuh)
(venetoclax tablets)

What is the most important information I should know about VENCLEXTA?
VENCLEXTA can cause serious side effects, including:
Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, and may lead to death. Your healthcare provider will do tests to check your risk of getting TLS before you start taking VENCLEXTA. You will receive other medicines before starting and during treatment with VENCLEXTA to help reduce your risk of TLS. You may also need to receive intravenous (IV) fluids into your vein. Your healthcare provider will do blood tests to check for TLS when you first start treatment and during treatment with VENCLEXTA. It is important to keep your appointments for blood tests. Tell your healthcare provider right away if you have any symptoms of TLS during treatment with VENCLEXTA, including:

- fever
- chills
- nausea
- vomiting
- confusion
- shortness of breath
- seizures
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain

Drink plenty of water during treatment with VENCLEXTA to help reduce your risk of getting TLS. Drink 6 to 8 glasses (about 56 ounces total) of water each day, starting 2 days before your first dose, on the day of your first dose of VENCLEXTA, and each time your dose is increased.
Your healthcare provider may delay, decrease your dose, or stop treatment with VENCLEXTA if you have side effects.
See "**What are the possible side effects of VENCLEXTA?**" for more information about side effects.

What is VENCLEXTA?
VENCLEXTA is a prescription medicine used:

- to treat adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- in combination with azacitidine, or decitabine, or low-dose cytarabine to treat adults with newly-diagnosed acute myeloid leukemia (AML) who:
  - are 75 years of age or older, **or**
  - have other medical conditions that prevent the use of standard chemotherapy.

It is not known if VENCLEXTA is safe and effective in children.

Who should not take VENCLEXTA?
Certain medicines must not be taken when you first start taking VENCLEXTA and while your dose is being slowly increased because of the risk of increased tumor lysis syndrome (TLS).

- **Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects.
- Do not start new medicines during treatment with VENCLEXTA without first talking with your healthcare provider.

Before taking VENCLEXTA, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have problems with your body salts or electrolytes, such as potassium, phosphorus, or calcium
- have a history of high uric acid levels in your blood or gout
- are scheduled to receive a vaccine. You should not receive a “live vaccine” before, during, or after treatment with VENCLEXTA, until your healthcare provider tells you it is okay. If you are not sure about the type of immunization or vaccine, ask your healthcare provider. These vaccines may not be safe or may not work as well during treatment with VENCLEXTA.
- are pregnant or plan to become pregnant. VENCLEXTA may harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with VENCLEXTA.

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- Females who are able to become pregnant should use effective birth control during treatment and for at least 30 days after the last dose of VENCLEXTA.
- If you become pregnant or think you are pregnant, tell your healthcare provider right away.

- are breastfeeding or plan to breastfeed. It is not known if VENCLEXTA passes into your breast milk. Do not breastfeed during treatment with VENCLEXTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects. See **"Who should not take VENCLEXTA?"**

How should I take VENCLEXTA?

- Take VENCLEXTA exactly as your healthcare provider tells you to take it. Do not change your dose of VENCLEXTA or stop taking VENCLEXTA unless your healthcare provider tells you to.
- When you first take VENCLEXTA:
  - You may need to take VENCLEXTA at a hospital or clinic to be monitored for TLS.
  - If you are taking VENCLEXTA for CLL or SLL, your healthcare provider will start VENCLEXTA at a low-dose. Your dose will be slowly increased weekly over 5 weeks up to the full dose. Read the **Quick Start Guide** that comes with VENCLEXTA before your first dose.
  - If you are taking VENCLEXTA for AML, your healthcare provider will start VENCLEXTA at a low-dose. Your dose will be slowly increased daily up to the full dose. Follow your healthcare provider's instructions carefully while increasing to the full dose.
- Follow the instructions about drinking water described in the section of this Medication Guide about TLS called **"What is the most important information I should know about VENCLEXTA?"** and also in the **Quick Start Guide**.
- Take VENCLEXTA 1 time a day with a meal and water at about the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break the tablets.
- If you miss a dose of VENCLEXTA and it has been less than 8 hours, take your dose as soon as possible. If you miss a dose of VENCLEXTA and it has been more than 8 hours, skip the missed dose and take the next dose at your usual time.
- If you vomit after taking VENCLEXTA, do not take an extra dose. Take the next dose at your usual time the next day.

What should I avoid while taking VENCLEXTA?

You should not drink grapefruit juice, eat grapefruit, Seville oranges (often used in marmalades), or starfruit while you are taking VENCLEXTA. These products may increase the amount of VENCLEXTA in your blood.

What are the possible side effects of VENCLEXTA?

VENCLEXTA can cause serious side effects, including:

- **See "What is the most important information I should know about VENCLEXTA?"**
- **Low white blood cell count (neutropenia).** Low white blood cell counts are common with VENCLEXTA but can also be severe. Your healthcare provider will do blood tests to check your blood counts during treatment with VENCLEXTA.
- **Infections**. Death and serious infections such as pneumonia and blood infection (sepsis) have happened during treatment with VENCLEXTA. Your healthcare provider will closely monitor and treat you right away if you have fever or any signs of infection during treatment with VENCLEXTA.

Tell your healthcare provider right away if you have a fever or any signs of an infection during treatment with VENCLEXTA.

The most common side effects of VENCLEXTA when used in combination with obinutuzumab or rituximab or alone in people with CLL or SLL include:

- low platelet counts
- low red blood cell counts
- diarrhea
- nausea
- upper respiratory tract infection
- cough
- muscle and joint pain
- tiredness
- swelling of your arms, legs, hands, and feet

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The most common side effects of VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine in people with AML include:

- nausea
- diarrhea
- low platelet counts
- constipation
- fever with low white blood cell counts
- low red blood cell counts
- infection in blood
- rash
- dizziness
- low blood pressure
- fever
- swelling of your arms, legs, hands, and feet
- vomiting
- tiredness
- shortness of breath
- bleeding
- infection in lung
- stomach (abdominal) pain
- pain in muscles or back
- cough
- sore throat

VENCLEXTA may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of VENCLEXTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VENCLEXTA?

- Store VENCLEXTA at or below 86°F (30°C).
- For people with CLL/SLL, keep VENCLEXTA tablets in the original package during the first 4 weeks of treatment. **Do not** transfer the tablets to a different container.

Keep VENCLEXTA and all medicines out of reach of children.

General information about the safe and effective use of VENCLEXTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VENCLEXTA for a condition for which it was not prescribed. Do not give VENCLEXTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about VENCLEXTA that is written for health professionals.

What are the ingredients in VENCLEXTA?

Active ingredient: venetoclax

Inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic.

The 10 mg and 100 mg coated tablets also include: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol, and titanium dioxide.

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For more information go to www.venclexta.com or call 1-800-633-9110

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