רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

Venclexta 10, 50 and 100 mg tablets

ונקלקסטה 10, 50 ו-100 מ"ג טבליות

Film coated tablets

Venetoclax 10, 50 and 100 mg

חברת AbbVie Biopharmaceuticals Ltd. מתכבדת להודיע כי משרד הבריאות אישר התוויה חדשה: **טיפול משולב של ונטוקלקס עם אובינוטוזומאב בחולי CLL/SLL שלא קיבלו טיפול קודם.** כמו כן, העלון לרופא והעלון לצרכן של התכשיר עודכנו.

בעלונים המצורפים מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה. שינויים המהווים החמרה מסומנים בצהוב, מידע שהתווסף מסומן באדום ומידע שהוסר מסומן ~~בכחול~~.

נוסח ההתוויה החדשה שאושרה:

VENCLEXTA is indicated for the treatment of:

1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA in combination with rituximab or as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), who have received at least one prior therapy.

VENCLEXTA in combination with obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

~~VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.~~

1.2 Acute Myeloid Leukemia

VENCLEXTA in combination with a hypomethylating agent or in combination with low dose cytarabine is indicated for newly diagnosed patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.

העלונים המעודכנים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd, רחוב החרש 4, הוד השרון או בטלפון 09 – 7909600.

בברכה,
אינה רגצקי - רוקחת ממונה

VENCLEXTA 10 MG TABLETS
VENCLEXTA 50 MG TABLETS
VENCLEXTA 100 MG TABLETS

QUALITATIVE AND QUANTITATIVE COMPOSITION

Venclexta 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of venetoclax.

Venclexta 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of venetoclax.

Venclexta 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of venetoclax.

For the full list of inactive ingredients, see section 11.

Education and Communication to potential prescribers
The marketing of Venclexta is subject to a risk management plan (RMP). Prescribers of this product should undergo education and training regarding the product emphasizing important safety information.

Patient Quick Start Guide
The 'Patient Quick Start Guide', includes instructions regarding the correct medication schedule and safety information for CLL/SLL Patients. Please explain to the patient the need to review the guide before starting treatment. The 'Patient Quick Start Guide' is included in the 'CLL/SLL Starting Pack'.

~~VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.~~
VENCLEXTA in combination with rituximab or as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), who have received at least one prior therapy.

VENCLEXTA in combination with obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

1.2 Acute Myeloid Leukemia

VENCLEXTA in combination with a hypomethylating agent or in combination with low dose cytarabine is indicated for newly diagnosed patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.

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

~~All~~ VENCLEXTA dosing~~e regimens~~ 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
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	
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 • 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.

- 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 Dosage 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.
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		
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)]*.

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

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)]*.

Concomitant use of preparations containing St. John’s wort

Hypersensitivity to the active substance venetoclax, or to any of the excipients listed in section ~~within the formulation. [see DESCRIPTION (11)]~~.

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 ~~T~~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% ~~of patients treated with VENCLEXTA in combination with rituximab (see Table 10). Grade 3 or 4 neutropenia developed in 63% of patients and Grade 4 neutropenia developed in~~ to 33% of patients treated with VENCLEXTA in combination and monotherapy studies (see Table 10, 12, 14). Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and ~~with rituximab and in 6% of patients treated with VENCLEXTA~~ monotherapy studies *[see Adverse Reactions (6.1)]*.

In patients with AML, ~~B~~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.

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 ~~the recommended~~ 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)]*.

5.65 Effects on ability to drive and use machines

Fatigue has been reported in some patients taking VENCLEXTA and should be considered when assessing a patient's ability to drive or operate machines.

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 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma ~~CLL/SLL~~

CLL14

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 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.				

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.

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~~Table 9~~ and Table 12~~Table 10~~ 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~~9~~. 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

Adverse Reaction by Body System	VENCLEXTA + Rituximab Followed by Single Agent VENCLEXTA (N=194)		Bendamustine + Rituximab (N=188)	
	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
Metabolism and nutrition disorders				
Tumor lysis syndrome	3	3	1	1
[a]Includes multiple adverse reaction terms.				

Other adverse reactions (all ~~G~~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 ~~g~~Grade 3 or 4 adverse reactions (≥2% patients) were neutropenia (12%) and anemia (3%).

Laboratory Abnormalities

~~Table 10~~ Table 12 describes common treatment-emergent laboratory abnormalities identified in the MURANO trial.

Table 1~~0~~2. Common (≥10%) New or Worsening Laboratory Abnormalities Occurring at ≥5% (Any Grade) or ≥2% (Grade 3 or 4) Higher Incidence with VEN+R ~~c~~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
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~~1~~.

Table 13~~1~~. 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

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

Table 142. 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 ~~Table 10~~.

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~~Acute Myeloid Leukemia

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).

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 13~~.

Table 15~~3~~. 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
	Thrombocytopenia[a]	49	45	54	54
	Neutropenia[a]	49	49	38	38

Blood and lymphatic system disorders	Febrile neutropenia	36	36	69	69
	Anemia[a]	30	30	15	15
Gastrointestinal disorders	Nausea	58	1	46	0
	Diarrhea	54	3	38	8
	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 14~~ Table 16 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 1~~6~~4. 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.

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 15~~.

Table 17~~5~~. 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 16~~ Table 18 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 1~~6~~8. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the

National Regulation by using an online form

~~http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formT ype=AdversEffectMedic@moh.gov.il~~

https://sideeffects.health.gov.il

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)]*.

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. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see *Contraindications (4)*)

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 ~~the recommended~~ 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.

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 ~~the recommended~~ 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 (~~5.4~~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)]*.

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~~overall~~ differences in safety and effectiveness were observed between older and younger patients in ~~MURANO~~ the combination and ~~the~~ 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*)]*.

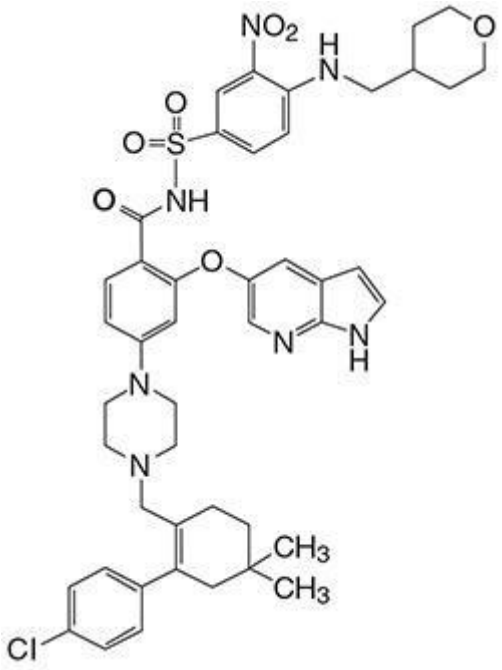
No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr ≥ 30 mL/min *[see Clinical Pharmacology (*12.3*)]*. A recommended dose has not been determined for patients with severe renal impairment (CLcr < 30 mL/min) or patients on dialysis.

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.

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.

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)]*.

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 Cmax, respectively, compared with venetoclax 400 mg administered alone. The venetoclax AUC24 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_{inf} ~~∞~~ 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 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~~the recommend~~ 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 Eastern Cooperative Oncology Group (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).

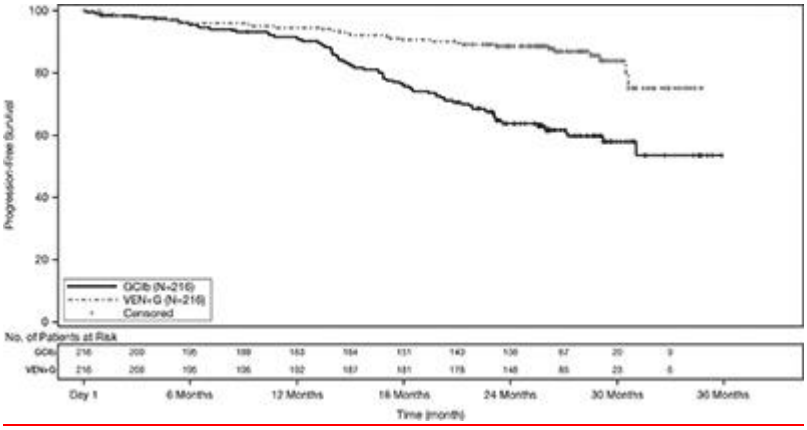
Efficacy results for CLL14 are shown in Table 19. The Kaplan-Meier curve for PFS is shown in Figure 1.

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.

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)
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 to 85 years), 97% were white, 74% were male, and 99% had ECOG performance status <2. Median prior lines of therapy was 1 (range: 1 to 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 17.~~ Table 21. The Kaplan-Meier curve for PFS is shown in Figure ~~1~~2.

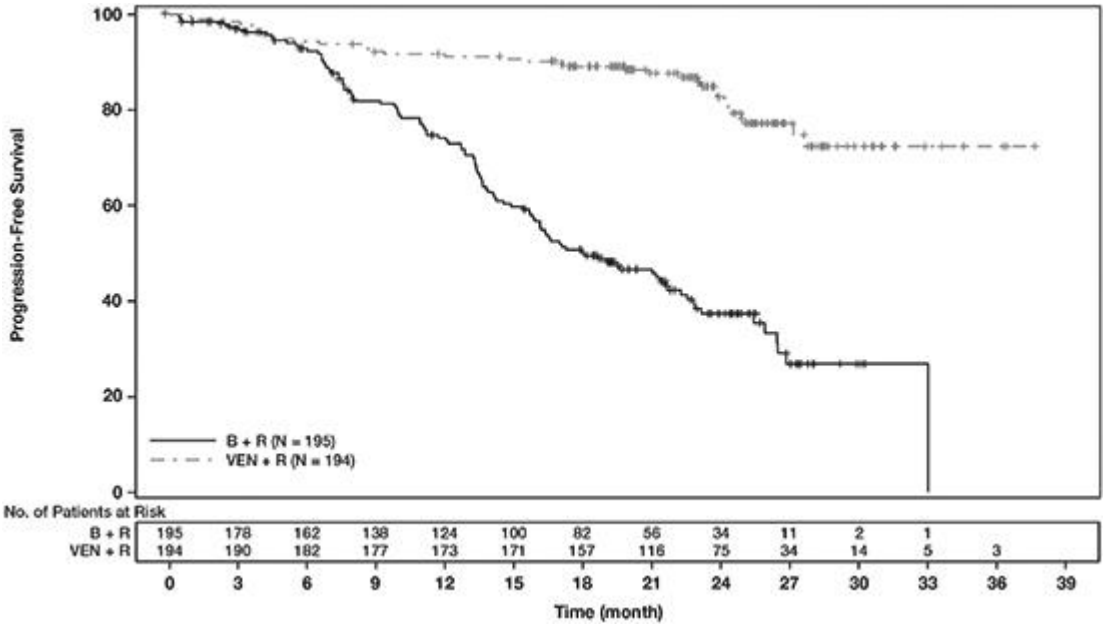
Table 21~~17~~. IRC-Assessed Efficacy Results in MURANO

Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Progression-free survival[a]		
Number of events, n (%)	35 (18)	106 (54)
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 ~~R~~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~~1~~. 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.

~~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.~~ 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 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~~Table 18~~ summarizes the baseline demographic and disease characteristics of the study population.

Table 22~~18~~. 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 1 2	 40 52 8
Tumor burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50 53
Number of prior therapies; median (range)	2.5 (1-10)
Time since diagnosis, years; median (range)[a]	6.6 (0.1-32.1)
ECOG = Eastern Cooperative Oncology Group. [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 ~~Table 19~~.

Table 23~~19~~. 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 (%) CR, n (%) CRi, n (%)	8 (8) 6 (6) 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~~ Minimal residual disease 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 71.7 ~~50.1~~ months).

The median age was 65~~6~~ 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 and~~. As~~ assessed by an IRC.~~,~~ ~~t~~The ORR was 76~~1~~% (95% CI: 64~~58~~%, 86~~2~~%), CR + CRi rate was 10~~7~~%, and PR rate was 66~~4~~%. The median DOR was 36.2 months (range: 2.4 to 52.4 months).

~~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%.~~

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 19.514.3 months (range: 0.1 to 31.439.5 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 and was assessed by an. Based on IRC. assessment, the The ORR was 70% (95% CI: 61%, 78%), with a CR + CRi rate of 51%, and PR rate of 659%. The median DOR was not reached with a median follow-up time of 19.9 months (range: 2.9 to 36 months).

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 years 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~~Table 20~~ summarizes the baseline demographic and disease characteristics of the study population.

Table 24~~20~~. 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 2 3	 64 33 3	 92 8 0
Disease history; % *De Novo* AML Secondary AML	 73 27	 85 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

ECOG = Eastern Cooperative Oncology Group.
[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.

The efficacy results are shown in Table 25 ~~Table 21~~.

Table 25~~1~~. 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.

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 years or older or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria ~~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 ~~Table 22~~ summarizes the baseline demographic and disease characteristics of the study population.

Table 2~~2~~6~~2~~. 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 2 3	 66 33 1.6
Disease history, % *De novo* AML Secondary AML	 54 46
Mutation analyses detected[a]; %	
TP53	8
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
ECOG = Eastern Cooperative Oncology Group. [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 273.

Table 273. 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 0N = 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).

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
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)
Wallet containing 10 mg tablets	14 x 10 mg tablets
Wallet containing 50 mg tablets	7 x 50 mg tablets

Unit ~~D~~dose blister containing 10 mg tablets	2 x 10 mg tablets
Unit ~~D~~dose blister containing 50 mg tablet	1 x 50 mg tablet
Unit ~~D~~dose blister containing 100 mg tablet	1 x 100 mg tablet
Bottle containing 100 mg tablets	120 x 100 mg tablets

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 30°C.

The expiry date of the product is indicated on the packaging materials

17 MANUFACTURER

AbbVie Inc., North Chicago, IL 60064, USA

18 MARKETING AUTHORISATION HOLDER

AbbVie Biopharmaceuticals Ltd, 4 Hacharash St., Hod Hasharon, Israel.

19 MARKETING AUTHORISATION NUMBERS

VENCLEXTA 10 MG TABLETS 158-19-34868
VENCLEXTA 50 MG TABLETS 158-20-34869
VENCLEXTA 100 MG TABLETS 158-21-34870

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on March 2019, and it was updated according to the guidelines of the Ministry of Health on January 2020.

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו - 1986

התרופה משווקת על פי מרשם רופא בלבד

ונקלקסטה 10 מ"ג טבליות
ונקלקסטה 50 מ"ג טבליות
ונקלקסטה 100 מ"ג טבליות

טבליות מצופות

~~ה~~חומר ~~ה~~פעיל וכמותו:
כל טבליה מכילה:

ונקלקסטה 10 מ"ג טבליות	**ונקלקסטה 50 מ"ג טבליות**	**ונקלקסטה 100 מ"ג טבליות**
ונטוקלקס 10 מ"ג venetoclax	ונטוקלקס 50 מ"ג venetoclax	ונטוקלקס 100 מ"ג venetoclax

לרשימת החומרים הבלתי פעילים, נא ראה סעיף 6 "מידע נוסף" בעלון זה.

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך/ עבורך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם/ מצבם הרפואי דומה.

בנוסף לעלון, לתכשיר ונקלקסטה קיים מדריך מקוצר להתחלת הטיפול עבור חולי CLL/SLL. מדריך זה מכיל הנחיות חשובות בנוגע להתחלת הטיפול שעליך לדעת. יש לקרוא את המדריך המקוצר להתחלת הטיפול המצורף לאריזת 'CLL/SLL אריזה התחלתית' לפני השימוש בתכשיר. יש לשמור את המדריך לעיון נוסף במידת הצורך.

התרופה מיועדת לשימוש במבוגרים מעל גיל 18.

1.למה מיועדת התרופה?

ונקלקסטה, כטיפול יחיד או בשילוב עם ריטוקסימאב, מיועדת לטיפול בחולים עם לוקמיה לימפוציטית כרונית (Chronic Lymphocytic Leukemia [CLL]) או בחולים עם לימפומה של לימפוציטים קטנים ([Small Lymphocytic Lymphoma [SLL~~;~~
~~עם או ללא שינויים מסוימים ב- DNA הנקראים "מחיקה של 17p" ("17p deletion") ואשר~~ שקיבלו לפחות טיפול קודם אחד ~~לפני כן~~.
ונקלקסטה, בשילוב עם אובינוטוזומאב, מיועדת לטיפול בחולים שלא קיבלו טיפול קודם הסובלים מלוקמיה לימפוציטית כרונית (Chronic Lymphocytic Leukemia [CLL]) או בחולים עם לימפומה של לימפוציטים קטנים (Small Lymphocytic Lymphoma [SLL]).

ונקלקסטה בשילוב עם תכשירי היפומטילציה (hypomethylating agents) או בשילוב עם ציטרבין ~~(Cytarabine)~~ במינון נמוך (low-dose Cytarabine) מיועדת גם לטיפול בחולים שאובחנו לראשונה עם לוקמיה מיאלואידית חריפה (Acute Myeloid Leukemia [AML]), אשר אינם מתאימים לטיפול כימותרפי אינטנסיבי.

קבוצה תרפויטית: אנטינאופלסטי, מעכב BCL-2.

ונקלקסטה פועלת באמצעות עיכוב של חלבון בגוף הנקרא "BCL-2". זהו חלבון המסייע לתאי הסרטן לשרוד. חסימת חלבון זה מסייעת להשמיד ולהפחית את מספר תאי הסרטן. בנוסף, היא מאטה את החמרת המחלה.

2. לפני שימוש בתרופה

אין להשתמש בתרופה אם:

- אתה רגיש (אלרגי) לחומר הפעיל ~~ונטוקלקס~~ או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (~~מפורטים~~ לרשימת המרכיבים הבלתי פעילים, ראה ~~ב~~סעיף 6).
- אתה נוטל תרופה צמחית המוכרת בשם היפריקום (סנט ג'ונס וורט - St. John's wort) לטיפול בדיכאון.
- אתה חולה ב- CLL או SLL ונוטל תרופה אשר מעכבת אנזים CYP3A בצורה חזקה. **בעת התחלת הטיפול ובמהלך התקופה בה נעשית העלאה הדרגתית במינון** (בדרך כלל במשך 5 שבועות) משום שהסיכון ללקות בתסמונת מסוכנת בשם תסמונת פירוק הגידול ([TLS] Tumour Lysis Syndrome) יעלה כאשר נוטלים ונקלקסטה עם התרופות הללו.

חשוב שתספר לרופא שלך, לרוקח או לאחות על כל התרופות שאתה לוקח, כולל תרופות מרשם וללא מרשם, ויטמינים ותוספי תזונה צמחיים.

אין להתחיל נטילת תרופות חדשות במהלך הטיפול עם ונקלקסטה מבלי להתייעץ תחילה עם הרופא.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

לפני הטיפול ~~עם~~ב~~ונקלקסטה, ספר לרופא, לרוקח או לאחות~~ אם :

- הנך סובל מבעיות כלשהן בכליה, מאחר וייתכן כי הסיכון לתופעת לוואי בשם תסמונת פירוק הגידול (Tumour Lysis Syndrome [TLS]) יעלה
- יש לך בעיות במלחים או באלקטרוליטים בגופך, כגון אשלגן, זרחן, או סידן
- יש לך היסטוריה של רמות גבוהות של חומצה אורית בדם, או שיגדון
- אתה סבור שייתכן ויש לך זיהום או היה לך זיהום ממושך או חוזר
- אתה צפוי לקבל חיסון. אין להשתמש בחיסון המכיל תרכיב חי לפני, בתקופת הטיפול -או לאחר הטיפול עם ונקלקסטה ללא התייעצות מוקדמת עם הרופא המטפל
- הנך בהיריון, מתכנן היריון, מניקה או מתכנן להניק

אם אחד מהמצבים המתוארים מעלה תקף לגביך, או אם אינך בטוח, שוחח עם הרופא, הרוקח או האחות שלך לפני נטילת תרופה זו.

תסמונת פירוק הגידול ([TLS] Tumour Lysis Syndrome)
כתוצאה מפירוק מהיר של תאים סרטניים במהלך הטיפול, חולים מסוימים עלולים לפתח רמות חריגות של מלחים מסוימים (כגון אשלגן וחומצה אורית) בדם. מצב זה נקרא תסמונת פירוק הגידול ([TLS] Tumour Lysis Syndrome).

TLS יכולה לגרום לאי ספיקת כליות, לצורך בטיפול דיאליזה, הפרעות בקצב הלב, פרכוסים ועלולה להוביל למוות. הסיכון ל- TLS הוא ב~~- 5 ה~~שבועות הראשונים לטיפול עם ונקלקסטה.

הרופא שלך יבצע בדיקות דם לצורך הערכת הסיכון ל - TLS לפני שתתחיל לקחת ונקלקסטה.

ייתכן והרופא שלך ייתן לך גם תרופות אחרות לפני תחילת הטיפול עם ונקלקסטה ובמהלכו, על מנת לסייע בהפחתת הסיכון שלך לסבול מ- TLS.

שתייה מרובה של מים, לפחות 1.5 – 2 ליטרים (בערך 6 – 8 כוסות) ביום, החל מיומיים לפני מתן המנה הראשונה, ביום התחלת הטיפול וכל פעם שיש עלייה במינון, מסייעת בפינוי תוצרי הפירוק של תאי סרטן מגופך דרך השתן ויכולה להפחית את הסיכון שלך ל- TLS (ראה סעיף 3) . ~~ייתכן ותהיה זקוק לקבל נוזלים במתן תוך וריד.~~
ספר מיד לרופא, לרוקח או לאחות שלך, אם יש לך כל אחד מהתסמינים של TLS הרשומים בסעיף 4.
אם אתה נמצא בסיכון ל- TLS ייתכן שתטופל בבית חולים כדי שתוכל לקבל נוזלים לתוך הוריד במקרה הצורך, לעבור בדיקות דם לעיתים קרובות יותר ולהיבדק להופעת תופעות לוואי. זאת כדי לבדוק אם תוכל להמשיך לקחת ונקלקסטה באופן בטוח.

ילדים ומתבגרים
התכשיר מיועד לשימוש במבוגרים . זאת משום שהתרופה לא נבדקה בילדים ומתבגרים.

~~ונקלקסטה ותרופות אחרות~~אינטראקציות/תגובות בין תרופתיות

ספר לרופא או לרוקח אם אתה לוקח, אם לקחת לאחרונה, או ייתכן ותיקח תרופות אחרות. זה כולל תרופות ללא מרשם, תרופות צמחיות ותוספי תזונה. זאת משום שונקלקסטה עלולה להשפיע על אופן פעולתן של תרופות מסוימות. כמו כן, תרופות מסוימות יכולות להשפיע על האופן שבו ונקלקסטה פועלת ולגרום לתופעות לוואי חמורות.

ספר לרופא או לרוקח שלך אם אתה לוקח אחת מהתרופות הבאות משום שהן יכולות להעלות או להפחית את הכמות של ונקלקסטה בדמך:

- תרופות לזיהומים פטרייתיים - קטוקונאזול, איטראקונאזול, פלוקונאזול, וריקונאזול, או פוסאקונאזול
- אנטיביוטיקה לטיפול בזיהומים חיידקיים - קלאריתרומיצין, ציפרופלוקסצין, אריתרומיצין, נאפצילין או ריפאמפיצין
- תרופות למניעת התקפי עוויתות או לטיפול באפילפסיה – קארבאמאזפין, פניטואין
- תרופות לזיהום HIV– אפאבירנז, אטראבירין, ריטונאביר
- תרופות לטיפול בלחץ דם גבוה או בתעוקת חזה – וראפאמיל, דילטיאזם, קאפטופריל, קארבדילול, פלודיפין, רנולזין
- תרופה המשמשת לטיפול במצב ריאתי הנקרא יתר לחץ דם ריאתי - בוסנטן
- תרופה לטיפול בהפרעת שינה (נרקולפסיה) המוכרת בשם מודפיניל
- תרופה צמחית המוכרת בשם היפריקום (סנט ג'ונס וורט - St. John's wort)
- תרופות לטיפול בהפרעות בקצב הלב – דרונדרון, אמיודרון, כינידין
- תרופה למניעת קרישי דם – טיקגרלור
- תרופה המשמשת למניעת דחיית איברים – ציקלוספורין
- תוסף תזונה נוגד חימצון – קוורציטין

ייתכן והרופא שלך ישנה את המינון שלך עבור ונקלקסטה.

ספר לרופא אם אתה לוקח אחת מהתרופות הבאות משום שונקלקסטה עלולה להשפיע על אופן פעולתן:

- תרופה למניעת קרישי דם – ורפארין
- תרופה המשמשת לטיפול בבעיות לב המוכרת בשם דיגוקסין
- תרופה לסרטן המוכרת בשם אברולימוס
- תרופה המשמשת למניעת דחיית איברים המוכרת בשם סירולימוס

שימוש בתרופה ומזון~~נטילת ונקלקסטה עם מזון ושתייה~~
אין לאכול מוצרים המכילים אשכוליות, תפוזי סביליה (תפוזים מרים המשמשים לעיתים קרובות להכנת ריבות), או פרי כוכב (קרמבולה) במהלך הטיפול עם ונקלקסטה - זה כולל אכילתם, שתיית המיץ או נטילת תוסף תזונה אשר עשוי להכיל אותם. זאת משום שהם יכולים להעלות את כמות ונקלקסטה בדמך.

היריון

- אם את בהיריון, חושבת שייתכן ואת בהיריון או מתכננת להרות, יש ליידע את הרופא שלך, הרוקח או האחות לפני נטילת תרופה זו.
- ונקלקסטה עלולה לפגוע בעובר שלך.

אמצעי למניעת היריון

- לפני תחילת הטיפול בונקלקסטה, הרופא שלך יבקש ממך לבצע בדיקה לשלילת היריון. נשים בגיל הפוריות צריכות להשתמש באמצעי מניעה יעיל ביותר במהלך הטיפול ובמשך תקופה של לפחות 30 יום לאחר סיום הטיפול בונקלקסטה כדי להימנע מכניסה להיריון.
- ספרי לרופא מיד אם נכנסת להיריון במהלך הטיפול עם תרופה זו.

הנקה
אם את מניקה או מתכננת להניק. לא ידוע אם הרכיב הפעיל בונקלקסטה עובר לחלב אם. אין~~על כן לא מומלץ~~ להניק במהלך הטיפול עם תרופה זו.

פוריות
ונקלקסטה עלולה לגרום לעקרות בגברים (ספירת זרע נמוכה או העדר זרע). הדבר עלול להשפיע על יכולתך להפוך לאב לילד. התייעץ עם הרופא לפני התחלת הטיפול עם ונקלקסטה.

נהיגה ושימוש במכונות
ייתכן ותחוש בעייפות לאחר נטילת ונקלקסטה, שיכולה להשפיע על יכולתך לנהוג או להפעיל מכונות.

3. כיצד תשתמש בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר. המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

ייתכן ותידרש התאמה של המינון בגלל תופעות לוואי או משיקולים אחרים.
יתכן ותצטרך לקחת ונקלקסטה בבית חולים כדי לעקוב אחר תסמונת פירוק הגידול (TLS).

עבור חולי CLL או SLL

המינון המקובל בדרך כלל הוא:
אתה תתחיל את הטיפול בונקלקסטה במינון נמוך למשך שבוע אחד. הרופא שלך יעלה בהדרגה את המינון במהלך 5-4 השבועות הבאים עד למינון המלא המקובל. קרא את המדריך המקוצר להתחלת הטיפול, המצורף לונקלקסטה לפני המנה הראשונה שלך.

- המינון ההתחלתי הוא 20 מ"ג (שתי טבליות של 10 מ"ג) פעם ביום למשך 7 ימים.
- המינון יוגדל ל- 50 מ"ג (טבליה אחת של 50 מ"ג) פעם ביום למשך 7 ימים.
- המינון יוגדל ל- 100 מ"ג (טבליה אחת של 100 מ"ג) פעם ביום למשך 7 ימים.
- המינון יוגדל ל- 200 מ"ג (שתי טבליות של 100 מ"ג) פעם ביום למשך 7 ימים.
- המינון יוגדל ל- 400 מ"ג (ארבע טבליות של 100 מ"ג) פעם ביום למשך 7 ימים.
    - כאשר אתה מקבל רק ונקלקסטה, אתה תמשיך לקבל מינון של 400 מ"ג ליום, שהוא המינון המקובל, למשך כל הזמן שיידרש.
    - כאשר אתה מקבל ונקלקסטה בשילוב עם ריטוקסימאב, אתה תקבל את המינון של 400 מ"ג ליום, למשך 24 חודשים.
    - כאשר אתה מקבל ונקלקסטה בשילוב עם אובינוטוזומאב, אתה תקבל את המינון של 400 מ"ג ליום, למשך 12 חודשים.

עבור חולי AML בשילוב עם התכשירים אזאציטידין (azacitidine) או דסיטבין (decitabine)

המינון המקובל בדרך כלל הוא:

אתה תתחיל את הטיפול בונקלקסטה במינון נמוך. הרופא שלך יעלה בהדרגה את המינון במהלך 3 הימים הבאים עד למינון המלא המקובל. מלא אחר הוראות הרופא בקפידה במהלך עלית המינון עד הגעה למינון המקובל.

- המינון ההתחלתי הוא 100 מ"ג (טבליה אחת של 100 מ"ג) פעם ביום למשך יום 1.
- המינון יוגדל ל-200 מ"ג (שתי טבליות של 100 מ"ג) פעם ביום למשך יום 1.
- המינון יוגדל ל- 400 מ"ג (ארבע טבליות של 100 מ"ג) פעם ביום. אתה תמשיך לקבל מינון של 400 מ"ג ליום, שהוא המינון המקובל, למשך כל הזמן שיידרש.

עבור חולי AML בשילוב עם מינון נמוך של ציטרבין (low-dose cytarabine)

המינון המקובל בדרך כלל הוא:

אתה תתחיל את הטיפול בונקלקסטה במינון נמוך. הרופא שלך יעלה בהדרגה את המינון במהלך 4 הימים הבאים עד למינון המלא המקובל. מלא אחר הוראות הרופא בקפידה במהלך עלית המינון עד הגעה למינון המקובל.

- המינון ההתחלתי הוא 100 מ"ג (טבליה אחת של 100 מ"ג) פעם ביום למשך יום 1.
- המינון יוגדל ל-200 מ"ג (שתי טבליות של 100 מ"ג) פעם ביום למשך יום 1.
- המינון יוגדל ל-400 מ"ג (ארבע טבליות של 100 מ"ג) פעם ביום למשך יום 1.
- המינון יוגדל ל-600 מ"ג (שש טבליות של 100 מ"ג) פעם ביום. אתה תמשיך לקבל מינון של 600 מ"ג ליום, שהוא המינון המקובל, למשך כל הזמן שיידרש.

אין לעבור על המנה המומלצת.

כיצד יש לקחת ונקלקסטה

- יש לקחת את הטבליות עם ארוחה, בערך באותה השעה בכל יום
- יש לבלוע את הטבליות בשלמותן עם כוס מים
- אין ללעוס, לכתוש, או לשבור את הטבליות

~~במקרה שתקיא לאחר שלקחת ונקלקסטה, אין לקחת מנה נוספת באותו היום. יש לקחת את המנה הבאה בזמן הרגיל למחרת. אם יש לך קושי בלקיחת ונקלקסטה, שוחח עם הרופא.~~

הנחיות להוצאת הטבליות מתוך הבליסטר:
1. פתח את חפיסת הטבליות.
2. משוך את כיסוי הטבליה היומית (מסומן עם חץ △ועם מספרו של היום).
3. דחוף את הטבליה כלפי מטה.

הטבליה תצא מהצד הנגדי של החפיסה.

יש לשתות הרבה מים
חשוב מאוד שתשתה הרבה מים במהלך הטיפול עם ונקלקסטה כדי להפחית מהסיכון לתסמונת פירוק הגידול (TLS).

עליך להתחיל לשתות לפחות 1.5 – 2 ליטרים של מים (בערך 6 – 8 כוסות) ביום, יומיים לפני תחילת הטיפול עם ונקלקסטה. בכמות זו ניתן לכלול משקאות ללא אלכוהול וללא קפאין, אך יש להימנע ממיצים של אשכוליות, תפוזי סביליה, או פרי כוכב (קרמבולה). עליך להמשיך לשתות לפחות 1.5 – 2 ליטרים של מים (בערך 6 – 8 כוסות) ביום בו אתה מתחיל טיפול עם ונקלקסטה. שתה כמות דומה של מים (לפחות 1.5 – 2 ליטרים ביום) יומיים לפני וביום בו המינון שלך יעלה.

אם הרופא שלך סבור שאתה נמצא בסיכון ל- TLS, ייתכן שתטופל בבית חולים כדי שתוכל לקבל נוזלים נוספים לתוך הווריד במקרה הצורך, לעבור בדיקות דם לעיתים קרובות יותר ולהיבדק להופעת תופעות לוואי. זאת כדי לבדוק אם תוכל להמשיך לקחת ונקלקסטה באופן בטוח.

אם נטלת בטעות מינון גבוה יותר
אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים והבא אריזת התרופה איתך.

אם שכחת לקחת ונקלקסטה
- אם עברו פחות מ- 8 שעות מהמועד בו אתה בדרך כלל נוטל את המנה שלך, קח את המנה בהקדם האפשרי.
- אם עברו יותר מ- 8 שעות מהמועד בו אתה בדרך כלל נוטל את המנה שלך, אל תיקח את המנה ביום הזה. חזור ללוח זמני נטילת המנות הרגיל שלך למחרת.
- אם הקאת לאחר נטילת ונקלקסטה, אל תיקח מנה נוספת. חזור ללוח זמני נטילת המנות הרגיל שלך למחרת.
- אם אינך בטוח, פנה לרופא, לרוקח או לאחות שלך.

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.

אין להפסיק לקחת ונקלקסטה
גם אם חל שיפור במצב בריאותך, אין להפסיק הטיפול בתרופה ללא התייעצות עם הרופא.

- **אין לקחת תרופות בחושך! בדוק את התווית והמנה <u>בכל פעם</u> שהנך לוקח תרופה. הרכב משקפיים אם הנך זקוק להם.**

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

4. <u>תופעות לוואי</u>

כמו בכל תרופה, השימוש בונקלקסטה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן שלא תסבול מאף אחת מהן.

תסמונת פירוק הגידול ([TLS] Tumour Lysis Syndrome) (שכיחות - עלולות להשפיע על עד 1 מתוך 10 אנשים):
הפסק לקחת ונקלקסטה ופנה מיד לעזרה רפואית אם אתה מבחין באחד מהתסמינים של TLS:
- חום או צמרמורות
- הרגשת חולי (בחילות או הקאות)
- הרגשת בלבול
- תחושה של קוצר נשימה
- קצב לב לא סדיר
- שתן כהה או עכור
- הרגשת עייפות יוצאת דופן
- כאבי שרירים או אי נוחות במפרקים
- התקפי עוויתות או פרכוסים

ספירה נמוכה של תאי דם לבנים (נויטרופניה) (שכיחות מאוד - עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)**:** ספירה נמוכה של תאי דם לבנים נפוצה במהלך הטיפול בונטוקלקס אך יכולה להיות חמורה. הרופא יבדוק את ספירת הדם שלך במהלך הטיפול עם ונקלקסטה. ~~ספר לרופא מיד אם מופיעים אצלך סימנים של זיהום במהלך הטיפול עם ונקלקסטה.~~

זיהום: מוות וזיהום חמור כמו דלקת ריאות וזיהום בדם (אלח דם) קרו במהלך הטיפול עם ונקלקסטה. הרופא שלך יבצע מעקב קפדני יותר ויטפל בך מיד אם יש לך חום או כל סימן של זיהום במהלך הטיפול עם ונקלקסטה.

ספר לרופא אם אתה מבחין באחת מתופעות הלוואי הבאות:

בחולי CLL או SLL

שכיחות מאוד (עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)

- זיהום בדרכי הנשימה העליונות - הסימנים כוללים נזלת, כאב גרון או שיעול
- שלשול
- הרגשת חולי (בחילות או הקאות)
- עצירות
- הרגשת עייפות
- שיעול
- כאבי שרירים או מפרקים
- נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים
- חוסר שינה
- כאב ראש
- פריחה
- חום
- דלקת בדרכי הנשימה התחתונות
- כאבי בטן
- דלקת וכאב של רקמות הפה, הוושט והמעי (mucositis)
- סחרחורת
- קוצר נשימה
- דלקת ריאות

בנוסף, ניתן לראות בבדיקות דם:

- ספירה נמוכה של תאי דם אדומים (אנמיה)
- ספירה נמוכה של תאי דם לבנים (נויטרופניה, לימפופניה או לויקופניה בפרט)
- עלייה ברמות מלחי גוף (אלקטרוליט) ~~הנקרא~~ הכוללים פוספאט ~~זרחן~~, אשלגן או נתרן
- ירידה ברמות מלחי הגוף (אלקטרוליט) הכוללים פוספאט, אשלגן, סידן או נתרן
- ספירה נמוכה של טסיות
- רמות גבוהות של אנזימי כבד הנקראים פוספטאזה בסיסית (alkaline phosphatase [ALP])
- רמות גבוהות של אנזימי כבד הנקראים אספרטט אמינו טרנספראז (aspartate aminotransferase [AST/GOT])
- רמות גבוהות של סוכר בדם
- רמות נמוכות של סוכר בדם
- רמות נמוכות של חלבון הנקרא אלבומין
- רמות גבוהות של חלבון הנקרא בילירובין
- רמות גבוהות של חומצה אורית
- רמות גבוהות של קראטינין בדם

שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים)

- ~~דלקת ריאות~~
- חום עם ספירה נמוכה של תאי דם לבנים (חום נויטרופני)
- זיהום חמור בדם (אלח דם)
- דלקת בדרכי השתן

בנוסף, ניתן לראות בבדיקות דם:

- ~~עלייה ברמת אוריאה~~
- עלייה ברמות מלחי גוף (אלקטרוליטים) הכוללים סידן ומגנזיום ~~אשלגן~~
- ~~ירידה ברמת סידן~~
- ~~ספירה נמוכה של תאי דם לבנים הנקראים לימפוציטים~~

<u>בחולי AML</u>

שכיחות מאוד (עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)
- הרגשת חולי (בחילות או הקאות)
- שלשול
- עצירות
- נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים
- הרגשת עייפות
- דלקת ריאות
- חום עם ספירה נמוכה של תאי דם לבנים (חום נויטרופני)
- זיהום חמור בדם (אלח דם)
- פריחה
- דימום
- קוצר נשימה
- כאב בטן
- סחרחורת
- שיעול
- כאבי גב או שרירים
- לחץ דם נמוך
- כאב גרון ופה
- חום
- ~~בצקת פריפריאלית~~
- זיהום בדרכי השתן
- צלוליטיס
- חוסר בחמצן שמועבר לרקמות הגוף (היפוקסיה)
- ~~דימום (Hemorrhage)~~
- לחץ דם גבוה
- זיהום הקשור במכשיר (Device related infection)
- תאבון מופחת

בנוסף, ניתן לראות בבדיקות דם:
- ספירה נמוכה של טסיות
- ספירה נמוכה של תאי דם לבנים (באופן כללי, ונויטרופניה או לימפופניה, באופן ספציפי)
- ספירה נמוכה של תאי דם אדומים (אנמיה)
- רמות גבוהות של סוכר בדם
- ירידה ברמות מלחי גוף (אלקטרוליטים) הכוללים סידן, נתרן, אשלגן, ~~זרחן~~ פוספאט אנאורגני, ~~או~~ מגנזיום או ביקרבונט
- רמות נמוכות של חלבון הנקרא אלבומין
- רמות גבוהות של בילירובין כללי
- רמות גבוהות של קראטינין בדם

שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים)

- ירידה במסת שריר (כיחשון [Cachexia])
- אברי גוף אינם פועלים כראוי תסמונת כשל בתפקוד איברים (Multiple organ dysfunction syndrome)
- זיהום מקומי

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם הרופא.

דיווח על תופעות לוואי
ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי,
או ע"י כניסה לקישור :

https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

https://sideeffects.health.gov.il

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי אריזת הקרטון. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- באריזת בקבוק, ניתן להשתמש בטבליות ונקלקסטה במשך 6 שבועות לאחר פתיחה ראשונה. **אין** להעביר את הטבליות לקופסה המיועדת לטבליות או למיכל אחר.
- יש לאחסן בטמפ' של 30°c ומטה.
- אין להשליך תרופות כלשהן לביוב או לאשפה הביתית. שאל את הרוקח כיצד להשליך תרופות שאינן בשימוש. אמצעים אלו יעזרו לשמור על הסביבה.

6. מידע נוסף

מה מכילה ונקלקסטה

נוסף על החומר הפעיל, התרופה מכילה גם :

- הרכיבים הנוספים בליבת הטבליה הם:

Copovidone (K value 28), polysorbate 80, colloidal anhydrous silica, anhydrous dibasic calcium phosphate, sodium stearyl fumarate.

- הציפוי בצבע צהוב בהיר של טבלית ה- 10 מ"ג מכיל:

Iron oxide yellow (E172), polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.

- הציפוי בצבע בז' של טבלית ה- 50 מ"ג מכיל:

Iron oxide yellow (E172), iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.

- הציפוי בצבע צהוב בהיר של טבלית ה- 100 מ"ג מכיל:

Iron oxide yellow (E172), polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.

כיצד נראית ונקלקסטה ומה תוכן האריזה:

- ונקלקסטה 10 מ"ג טבליות מצופות הן בצבע צהוב בהיר, עגולות, קמורות משני הצדדים, מוטבעות עם "V" על צד אחד ועם "10" על הצד השני.
- ונקלקסטה 50 מ"ג טבליות מצופות הן בצבע בז', מוארכות, קמורות משני הצדדים, מוטבעות עם "V" על צד אחד ועם "50" על הצד השני.
- ונקלקסטה 100 מ"ג טבליות מצופות הן בצבע צהוב בהיר, מוארכות, קמורות משני הצדדים, מוטבעות עם "V" על צד אחד ועם "100" על הצד השני.

ונקלקסטה משווקת באריזות הבאות:

צורת אריזה	מספר הטבליות
CLL/SLL אריזה התחלתית	כל אריזה מכילה ארבע חפיסות בליסטרים (מגשיות) שבועיות: • שבוע 1 (14 x 10 מ"ג טבליות) • שבוע 2 (7 x 50 מ"ג טבליות) • שבוע 3 (7 x 100 מ"ג טבליות) • שבוע 4 (14 x 100 מ"ג טבליות)
חפיסת 10 מ"ג	14 x 10 מ"ג טבליות
חפיסת 50 מ"ג	7 x 50 מ"ג טבליות
יחידת מנה של 10 מ"ג	2 x 10 מ"ג טבליות
יחידת מנה של 50 מ"ג	1 x 50 מ"ג טבלית
יחידת מנה של 100 מ"ג	1 x 100 מ"ג טבלית
בקבוק 100 מ"ג	120 x 100 מ"ג טבליות

ייתכן כי לא כל גדלי האריזה ישווקו.

- בעל הרישום וכתובתו: AbbVie Biopharmaceuticals Ltd., רחוב החרש 4, הוד השרון, ישראל.
- שם היצרן וכתובתו: AbbVie Inc., צפון שיקגו, IL 60064, ארה"ב.
~~עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך: מרץ 2019, ועודכן בהתאם להוראות משרד הבריאות בתאריך: יולי 2019.~~
- מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:
ונקלקסטה 10 מ"ג טבליות 158-19-34868
ונקלקסטה 50 מ"ג טבליות 158-20-34869
ונקלקסטה 100 מ"ג טבליות 158-21-34870

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר ע"י משרד הבריאות בתאריך מרץ 2019, ועודכן בהתאם להוראות משרד הבריאות בתאריך ינואר 2020.