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 התוויות חדשות לתכשיר.
בעלונים המצורפים מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה (שינוי שהינו הוספה מסומן בקו תחתון, מחיקה מסומנת ב~~קו אמצעי~~).

נוסח ההתוויות החדשות שאושרו:

VENCLEXTA is indicated for the treatment of:

1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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**.**
~~patients with relapsed or refractory CLL who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor~~

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.

ונטוקלקס הינה טבליה מצופה המגיעה ב-3 מינונים: 10, 50 ו- 100 מ"ג.
ונטוקלקס נלקחת פעם ביום בבליעה.
המינון של ונטוקלקס לחולי CLL/SLL מתחיל ב- 20 מ"ג ביום ועולה בהדרגה ל- 400 מ"ג ביום.
המינון של ונטוקלקס לחולי AML כשניתן בשילוב עם azacitidine או decitabine מתחיל ב- 100 מ"ג ועולה בהדרגה ל- 400 מ"ג.
המינון של ונטוקלקס לחולי AML כשניתן בשילוב עם low-dose cytarabine מתחיל ב- 100 מ"ג ועולה בהדרגה ל- 600 מ"ג.

העלון המעודכן לצרכן נשלח למאגר 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'.

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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.
~~patients with relapsed or refractory CLL who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.~~

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 dose regimens begin 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

~~**Week**~~	**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. ~~Once the ramp-up phase is completed, the~~The 400 mg dose is achieved using 100 mg tablets supplied in bottles *[see How Supplied/Storage and Handling (16)]*.

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 [~~CrCl~~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 2~~ 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 ~~2~~3. Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL/SLL ~~From Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)~~

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 ~~at first dose of 20 mg and 50 mg~~ • ~~Pre-dose at~~ 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 ~~at first dose of 20 mg and 50 mg~~ • ~~Pre-dose at~~ For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CLcr~~CrCl~~ <80ml/min ~~at first dose of 20 mg and 50 mg~~; 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 ~~at~~ • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient ~~at~~ • 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 Dose Modifications Based on Toxicities

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Interrupt dosing or reduce dose for toxicities. ~~See Table 3 for dose modifications for hematologic and other toxicities related to VENCLEXTA,~~ see ~~and~~ Table 4 and Table 5 for ~~dose~~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 ~~when at~~ after completing the ~~daily dose of 400 mg~~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 43. 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 4 Table 5) *[see Dosage and*
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 4Table 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 4Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 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 Table 4 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the

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 45. Dose ~~Modification~~ 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 ~~and~~ 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.

~~Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp- up phase is contraindicated. Concomitant use of VENCLEXTA with strong CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during ramp-up phase *[see Contraindications (4)]*. For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% when *strong* CYP3A inhibitors must be used concomitantly.~~

~~Avoid concomitant use of VENCLEXTA with *moderate* CYP3A inhibitors or P-gp inhibitors. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENCLEXTA dose by at least 50%. Monitor these patients more closely for signs of toxicities *[see Dosage and Administration (2.3)]*.~~

Resume the VENCLEXTA dosage that was used prior to ~~initiating~~ concomitant use of a strong or moderate ~~the~~ 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)]*.

~~The recommendations for managing drug-drug interactions are summarized in Table 5.~~

Table 7~~5~~. Management of Potential VENCLEXTA Interactions with CYP3A and P-gp Inhibitors

~~Inhibitors~~Coadministered drug	Initiation and Ramp-Up Phase		Steady Daily Dose (After Ramp-Up Phase)[a]
~~Strong CYP3A inhibitor~~ Posaconazole	CLL/SLL	Contraindicated	~~Avoid inhibitor use or~~ R~~r~~educe ~~the~~ VENCLEXTA dose ~~by at least 75%~~ 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	
Moderate CYP3A inhibitor P-gp inhibitor	~~Avoid inhibitor use or reduce~~ Reduce the VENCLEXTA dose by at least 50%		
[a]In patients with CLL/SLL, consider alternative medications or reduce the VENCLEXTA dose as			

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~~6~~. 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 venetoclax, or to any of the excipients 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 ~~previously treated CLL with~~ high tumor burden when treated with VENCLEXTA *[see Adverse Reactions (6.1), 6.2)]*.

In patients with CLL, The current (5 week) dose ramp-up, TLS prophylaxis and monitoring, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with 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 ~~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 ~~(see Table 2)~~ and comorbidities. Reduced renal function ~~(CrCl <80 mL/min)~~ 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 ~~and P-gp inhibitors~~ increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and ~~may~~ 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 ~~occurred~~ developed in ~~41% (98/240)~~ 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 33% of patients treated with VENCLEXTA monotherapy (see Table 12). Febrile neutropenia occurred in 4% of patients treated with VENCLEXTA in combination with rituximab and in 6% of patients treated with VENCLEXTA monotherapy *[see Adverse Reactions (6.1)]*.

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 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.

5.4 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 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)]*.

5.5 Effects on ability to drive and use machines

~~VENCLEXTA has no or negligible influence on the 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 serious adverse events 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)]*

Because clinical trials are conducted under widely variable conditions, adverse event rates

observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience with CLL/SLL

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 9 and 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 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 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%)

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

Laboratory Abnormalities

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

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

	VENCLEXTA + Rituximab N=194	**Bendamustine + Rituximab N=188**

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

~~**6.13.1 Clinical Trial Experience**~~

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data ~~of 240 patients with previously treated CLL~~ from ~~two phase 2~~ three single-arm trials (M13-982, M14-032, and ~~one phase 1 trial.~~ M12-175). In the pooled dataset, consisting of 352 patients with previously treated CLL or SLL, the median age was 66 years (range: 2~~8~~9 to 85 years), ~~95~~93% were white, and 6~~8~~9% were male. The median number of prior therapies was 3 (range: 0~~1~~ to 1~~5~~2). The median duration of treatment with VENCLEXTA at the time of data analysis was ~~approximately~~ 14.5~~0.3~~ months (range: 0 to 50~~34.1~~ months). ~~Approximately 46%~~ Fifty-two percent of patients received VENCLEXTA for more than 60~~48~~ weeks.

~~The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue.~~

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%43.8% of patients, with. The the most frequent serious adverse reactions (≥2%) (≥5%) being were pneumonia (9%), febrile neutropenia (5%), pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and TLS sepsis (5%).

Discontinuations due to adverse reactions occurred Adverse reactions led to treatment discontinuation in 98.3% of patients, dose reduction in 13%, and dose interruption in 36%. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA. autoimmune hemolytic anemia.

Dosage adjustments due to adverse reactions occurred in 9.6% of patients. The most frequent adverse reactions reaction (≥5%) leading to dose reductions or interruptions was adjustments were neutropenia (8%)., febrile neutropenia, and thrombocytopenia.

Adverse reactions identifiedreported in these3 trials of patients with previously treated CLL using single -agent VENCLEXTA are presented in Table 117.

Table 117. Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3 or 4) of Patients with Previously Treated CLL/SLL (VENCLEXTA Monotherapy)

Body System	Adverse Reaction	Any Grade (%) N=35222 40	Grade ≥3 or 4 (%) N=352240
Blood and lymphatic system disorders	Neutropenia[a]	5045	4145
	Anemia[ab]	3329	18
	Thrombocytopenia[ae]	2922	1520
	Lymphopenia[a]	11	7
	Febrile neutropenia	65	65
Gastrointestinal disorders	Diarrhea	4335	<31
	Nausea	4233	<1
	Abdominal pain[a]	18	3
	Vomiting	165	<1
	Constipation	164	0<1
	Mucositis[a]	13	<1
General disorders and administration site conditions	Fatigue[a]	3221	42
	Edema[a]	22	2
	Pyrexia	186	<1
	Peripheral edema	11	<1
Infections and infestations	Upper respiratory tract infection[a]	3622	1
	Pneumonia[a]	148	85
	Lower respiratory tract infection[a]	11	2

~~Metabolism and nutrition disorders~~	~~Hypokalemia~~	~~12~~	~~4~~
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a]~~Back pain~~	~~10~~29	~~<1~~2
	Arthralgia	12	<1
Nervous system disorders	Headache	18~~5~~	<1
	Dizziness[a]	14	0
Respiratory, thoracic, and mediastinal disorders	Cough[a]	22~~13~~	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]~~Neutropenia/neutrophil count decreased~~Includes multiple adverse reaction terms. [b]~~Anemia/hemoglobin decreased.~~ [c]~~Thrombocytopenia/platelet count decreased.~~			

Laboratory Abnormalities

Table 12 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline. The most common (>5%) grade 4 laboratory abnormalities observed with VENCLEXTA monotherapy were hematologic laboratory abnormalities, including neutropenia (33%), leukopenia (11%), thrombocytopenia (15%), and lymphopenia (9%).

Table 12. 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. In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting dose, 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.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures *[see Dosage and Administration (2.1, 2.2)]*. In venetoclax clinical trials, patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x 10^9/L and any measurable lymph node ≥5 cm were hospitalized to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the ramp-up phase.

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 10.

Monotherapy Studies (M13-982 and M14-032)

In 168~~66~~ patients with CLL treated according to recommendations described in sections 2.1 and 2.2 ~~starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg~~, the rate of TLS was 2~~6~~% *[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~~CrCl~~ ≥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).

~~Laboratory abnormalities relevant to TLS observed in 66 patients with CLL who followed the dose ramp-up schedule and TLS prophylaxis measures are presented in Table 8.~~

~~Table 8. Adverse Reactions of TLS and Relevant Laboratory Abnormalities Reported in Patients with CLL~~

~~Parameter~~	**~~All Grades (%) N=66~~**	**~~Grade ≥3 (%) N=66~~**
~~Laboratory TLS[a]~~	~~6~~	~~6~~
~~Hyperkalemia[b]~~	~~20~~	~~2~~
~~Hyperphosphatemia[c]~~	~~15~~	~~3~~
~~Hypocalcemia[d]~~	~~9~~	~~3~~
~~Hyperuricemia[e]~~	~~6~~	~~2~~

~~[a]Laboratory abnormalities that met ≥2 of the following criteria 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.~~
~~[b]Hyperkalemia/blood potassium increased.~~
~~[c]Hyperphosphatemia/blood phosphorus increased.~~
~~[d]Hypocalcemia/blood calcium decreased.~~
~~[e]Hyperuricemia/blood uric acid increased.~~

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)]*.

~~Additional common (≥1/100 to <1/10) Drug reactions reported~~

~~Infections and infestations~~
~~*Urinary tract infection*~~

~~Blood and lymphatic system disorders~~
~~*Lymphopenia (Lymphopenia/lymphocyte count decreased)*~~

~~Investigations~~
~~*Blood creatinine increased*~~

6.2 Clinical Trial Experience with AML

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

VENCLEXTA in Combination with Azacitidine or Decitabine

Azacitidine

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

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

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

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

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 13.

Table 13. Adverse Reactions Reported in ≥30% (Any Grade) or ≥5% (Grade ≥3) of Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Body System	Adverse Reaction	VENCLEXTA in Combination with Azacitidine		VENCLEXTA in Combination with Decitabine	
		Any Grade (%) N = 67	Grade ≥3 (%) N = 67	Any Grade (%) N = 13	Grade ≥3 (%) N = 13
Blood and lymphatic system disorders	Thrombocytopenia[a]	49	45	54	54
	Neutropenia[a]	49	49	38	38
	Febrile neutropenia	36	36	69	69
	Anemia[a]	30	30	15	15
Gastrointestinal disorders	Nausea	58	1	46	0
	Diarrhea	54	3	38	8
	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	Back pain	15	0	31	0

and connective tissue disorders	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 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 14. 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 15.

Table 15. 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 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VENCLEXTA

~~Venetoclax is predominantly metabolized by~~

~~CYP3A4/5.~~

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)]*.

~~Concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole) at initiation and during ramp-up phase is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.~~

~~For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the VENCLEXTA dose that was used prior to~~

~~initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)]*.~~

~~Co-administration of ketoconazole increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Co-administration of ritonavir increased venetoclax Cmax by 2.4-fold and AUC by 7.9-fold.~~ Moderate CYP3A Inhibitors and P-gp Inhibitors

~~Avoid concomitant use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) or P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) with VENCLEXTA. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENCLEXTA dose by at least 50%. Monitor patients more closely for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)]*.~~

Resume the VENCLEXTA dosage~~dose~~ that was used prior to ~~the~~concomitant use with a strong or moderate ~~initiating the~~ CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.3, 2.4) ~~and Clinical Pharmacology (12.3)~~]*.

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

~~Co-administration of a single dose of rifampin, a P-gp inhibitor, increased venetoclax C_{max} by 106% and AUC_{∞} by 78%.~~

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 ~~(e.g., carbamazepine, phenytoin, rifampin,)~~ or moderate CYP3A inducers ~~(e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction *[see Clinical Pharmacology (12.3)]*~~. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see *Contraindications (4)*)

~~Co-administration of multiple doses of rifampin, a strong CYP3A inducer, decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%.~~

7.2 Effects of VENCLEXTA on Other Drugs

Warfarin

~~In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S- warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving 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 ~~s~~Substrates

~~*Administration of a single 100 mg dose of venetoclax with digoxin resulted in a 35% increase in digoxin C_{max} and a 9% increase in AUC_{∞}.*~~. ~~Therefore, co-administration of narrow therapeutic index P-gp substrates (e.g., digoxin, everolimus, and sirolimus) with VENCLEXTA should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA.~~

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 ~~human~~ data on ~~the use of~~ 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 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 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 ~~infants~~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) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Conduct pregnancy testing in ~~F~~females of reproductive potential ~~should undergo pregnancy testing~~ 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 164 previously treated patients with CLL evaluated for efficacy by an Independent Review Committee in Studies M13-982 and M12-175, 91 (55.5%) patients were ≥65 years of age and 28 (17.1%) patients were ≥75 years of age.~~

Of the 352~~240~~ patients with previously treated CLL/SLL evaluated for safety from 3 open-label trials~~, 58%~~ of VENCLEXTA monotherapy, 57% (201/352) were ≥65 years of age and 18~~7~~% (62/352) were ≥75 years of age.

No overall differences in safety and effectiveness were observed between older and younger patients in MURANO 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, p~~P~~atients with reduced renal function (CLcr~~CrCl~~ <80 mL/min, calculated by Cockcroft-Gault formula) ~~are at increased risk of TLS. These patients may~~ 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.

~~No specific clinical trials have been conducted in subjects with renal impairment. Less than 0.1% of radioactive VENCLEXTA dose was detected in urine. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 mL/min) based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.~~

~~8.7 Hepatic Impairment~~

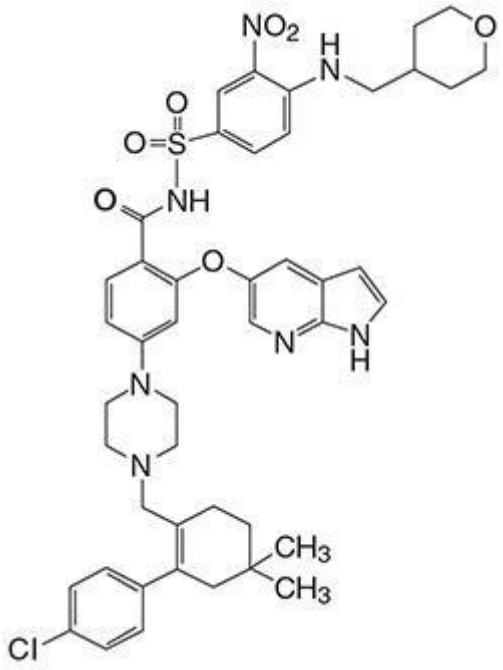
~~No specific clinical trials have been conducted in subjects with hepatic impairment, however human mass balance study showed that venetoclax undergoes hepatic elimination. Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*, a trend for increased adverse events was observed in patients with moderate hepatic impairment; monitor these patients more closely for signs of toxicity during the initiation and dose ramp-up phase. A recommended dose has not been determined for patients with severe hepatic impairment.~~

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

~~Following multiple oral administrations under fed conditions, m~~Maximum plasma concentration of venetoclax was reached 5~~-~~ to 8 hours following multiple oral administration under fed conditions ~~after dose. Venetoclax steady state AUC increased proportionally over~~

~~the dose range of 150-800 mg. Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 µg/mL and AUC_{0-24} was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose~~.

~~*Food* *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~~to~~ fasting conditions. ~~Venetoclax should be administered with a meal *[see Dosage and Administration (2.1)]*.~~

Distribution

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

Elimination

The ~~population estimate for the~~ terminal elimination half-life of venetoclax was approximately 26 hours. ~~The pharmacokinetics of venetoclax does not change over time.~~

Metabolism

~~*In vitro* studies demonstrated that~~ V~~v~~enetoclax is predominantly metabolized by CYP3A in vitro ~~4/5~~. ~~M27 was identified as a~~ The major metabolite identified in plasma, M27, has ~~with~~ 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 ~~administration of 200 mg~~ radiolabeled [^{14}C]-venetoclax 200 mg ~~dose~~ to healthy subjects, >99.9% of the dose was recovered in feces (20.8% as unchanged) and <0.1% ~~of the dose was excreted~~ in urine within 9 days~~, indicating that hepatic elimination is responsible for the clearance of venetoclax from the systemic circulation. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces~~.

Specific~~al~~ 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.

~~*Age, Race, Sex, and Weight*~~

~~Based on population pharmacokinetic analyses, age, race, sex, and weight do not have a clinically meaningful effect on venetoclax clearance.~~

~~*Renal Impairment*~~

~~Based on a population pharmacokinetic analysis that included 211 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min, calculated by Cockcroft-Gault equation), 83 subjects with moderate renal impairment (CrCl ≥30 and <60 mL/min) and 210 subjects with normal renal function (CrCl ≥90 mL/min), venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl <30 mL/min) or subjects on dialysis *[see Use in Specific Populations (8.6)]*.~~

~~*Hepatic Impairment*~~

~~Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic functi` `on. The NCI Organ Dysfunction Working Group criteria for hepatic impairment were used in the analysis. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 times ULN. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.~~

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, or rituximab.

Ketoconazole

~~Co-administration~~ Concomitant use of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) 400 mg once daily ~~ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor,~~ for 7 days ~~in 11 previously treated NHL patients~~ increased venetoclax C_{max} by ~~2.3-fold~~ 130% and AUC_{inf}~~∞~~ by ~~6.4-fold~~ 540% *[see Drug Interactions (7.1)]*.

Ritonavir

~~Co-administration of 50 mg once daily~~ Concomitant use of ritonavir (~~,~~ a strong CYP3A, P-gp and OATP1B1/B3 inhibitor) 50 mg once daily~~,~~ for 14 days ~~in 6 healthy subjects~~ increased venetoclax C_{max} by 140% ~~2.4-fold~~ and AUC by ~~7.9-fold~~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

C_{max}, respectively, compared with venetoclax 400 mg administered alone. The venetoclax AUC_{24} was 90% and 144% higher, respectively.

Rifampin ~~*multiple doses*~~

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%. ~~Co-administration of 600 mg once daily~~ Concomitant use of multiple doses of rifampin (as~~,~~ a strong CYP3A inducer) 600 mg once daily~~,~~ for 13 days ~~in 10 healthy subjects~~ decreased venetoclax C_{max} by 42% and AUC_{inf}~~∞~~ by 71% *[see Drug Interactions (7.1)]*.

~~*Rifampin single dose*~~

~~Co-administration of a 600 mg single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, in 11 healthy subjects increased venetoclax C_{max} by 106% and AUC_{∞} by 78% *[see Drug Interactions (7.1)]*.~~

~~*Azithromycin*~~

~~In a drug-drug interaction study in 12 healthy subjects, co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days decreased venetoclax Cmax by 25% and AUC∞ by 35%. No dose adjustment is needed when venetoclax is co-administered with azithromycin.~~

~~*Gastric Acid Reducing Agents*~~

~~Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability.~~

Warfarin

~~In a drug-drug interaction study in three healthy subjects, administration~~ Concomitant use of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R- warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

Digoxin

~~In a drug-drug interaction study in 10 healthy subjects, administration~~ Concomitant use of a single dose of venetoclax 100 mg ~~dose of venetoclax~~ with ~~0.5 mg~~ digoxin~~,~~ (a P-gp substrate)~~,~~ 0.5 mg increased ~~resulted in a 35% increase in~~ digoxin C_{max} by 35% and ~~and a 9% increase in~~ AUC_{inf}~~∞~~ by 9% [see Drug Interactions (*7.2*)].

In V~~v~~itro Studies

~~*In vitro* studies indicated that v~~Venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4~~ at clinically relevant concentrations~~.

Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1~~ *in vitro*, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding~~. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Venetoclax is ~~a P-gp and BCRP substrate as well as a P-gp and BCRP~~ an inhibitor and substrate of P-gp and BCRP and weak inhibitor of OATP1B1~~ inhibitor *in vitro*~~.

Venetoclax is not an ~~expected to~~ inhibitor of OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K ~~at clinically relevant concentrations~~.

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 the recommend dose.

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

MURANO

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

cycle was 28 days. Patients randomized to B+R received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles (28-day cycle) and rituximab at the above described dose and schedule.

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

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

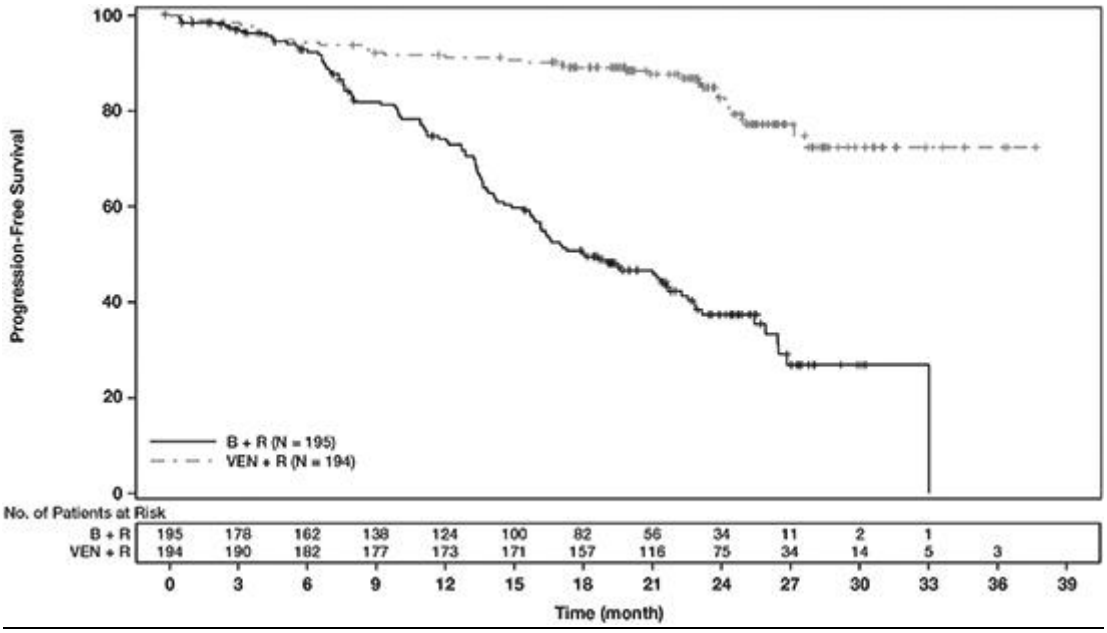
Efficacy results for MURANO are shown in Table 17. The Kaplan-Meier curve for PFS is shown in Figure 1.

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

Table 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)
[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 19.

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

Study M12-175

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

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

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

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

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

Study M14-032

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

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

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

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

14.2 **Acute Myeloid Leukemia**

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

comorbidity. Efficacy was established based on the rate of complete remission (CR) and the duration of CR.

Study M14-358

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

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

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

Table 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	64	92
2	33	8
3	3	0
Disease history; %		
De Novo AML	73	85
Secondary AML	27	15
Mutation analyses detected[a]; %		

TP53	21	31
IDH1 or IDH2	27	0
FLT-3	16	23
NPM1	19	15
Cytogenetic risk detected[b,c]; %		
Intermediate	64	38
Poor	34	62
Baseline comorbidities[d], %		
Severe cardiac disease	4.5	7.7
Severe pulmonary disease	1.5	0
Moderate hepatic impairment	9	0
Creatinine clearance <45 mL/min	13	7.7

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

The efficacy results are shown in Table 21.

Table 21. 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 or older or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the criterion: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr ≥30 to <45 mL/min or other comorbidity.

Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose *[see Dosage and Administration (2.1)]*. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m^2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1.

Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

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

Table 22. 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

[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 23.

Table 23. Efficacy Results for Patients with Newly-Diagnosed AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

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

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

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

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

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.

~~The approval for the use of VENCLEXTA in Chronic Lymphocytic Leukaemia (CLL) is based on phase 1 and phase 2 non-randomised trials. The results of a randomised, active-controlled phase 3 study are awaited.~~

~~The safety and efficacy of VENCLEXTA were established in 2 open-label, multicentre clinical trials of patients with CLL who had received at least one prior therapy, including those with deletion of the p13 locus on chromosome 17 (17p del).~~

tudy M13-982

Study M13-982 was a multicentre, single-arm open-label trial of 107 previously treated patients with CLL with 17p del. Table 9 summarises the baseline demographic and disease characteristics of the study population

Table 9. Baseline Patient Characteristics in Study M13-982

Characteristics	N = 107[a]
Age, years; median (range)	67 (37 to 85)
White; %	97.2
Male; %	65.4
ECOG performance status; %	39.3
0	
1	52.3
2	8.4
Tumour burden; %	
One or more nodes ≥5 cm	53.3
Number of prior therapies; median (range)	2 (1-10)
Time since diagnosis, months; median (range)[b]	81.7 (1.2-385.6)

[a] One patient did not harbour the 17p deletion.
[b] N=106.

~~Absolute lymphocyte count ≥25 x 10^9/L~~	~~50.5~~

Among the patients, 37.4% (34/91) were fludarabine refractory, 81.1% (30/37) had unmutated *IGHV*, and 23.8% (19/80) had 11q deletion.

In the study, patients with 17p del were identified using Vysis CLL FISH Probe Kit. Patients received VENCLEXTA via a weekly dose titration schedule starting at 20 mg and titrating 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. The median time on treatment at the time of evaluation was
12.1 months (range: 0 – 21.5
months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic

Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results for Study M13-982 are shown in Table 10.

Table 10. Efficacy Results in Study M13-982

	IRC Assessment (N=107)[a]	**Investigator Assessment (N=107)**
ORR, % (95% CI)	79.4 (70.5, 86.6)	73.8 (64.4, 81.9)
CR + CRi (%)	7.5	15.9
nPR (%)	2.8	3.7
PR (%)	69.2	54.2
DOR, % (95% CI) 12-month estimate	84.7 (74.5, 91.0)	89.1 (79.2, 94.4)

[a]One patient did not harbour the 17p deletion.

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

Median duration of response (DOR) or median progression-free survival (PFS) has not

been reached with approximately 12 months median follow-up.

Minimal residual disease (MRD) was evaluated using flow cytometry in 45 of 107 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. The cut-off for a negative status was one CLL cell per 10^4 leukocytes in the sample (i.e., an MRD value of $<10^{-4}$ was considered MRD negative). Seventeen percent (18/107) of patients were MRD negative in the peripheral blood, including six patients who were also MRD negative in the bone marrow

Study M12-175

Study M12-175 was a multicentre, open-label trial that enrolled previously treated patients with CLL, including those with 17p del. Efficacy was evaluated in 57 patients who had received a daily dose of 400 mg of VENCLEXTA following a dose titration schedule. Patients continued to receive 400 mg of VENCLEXTA monotherapy orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 11.5 months (range: 0.5 - 34.1 months). Table 11 summarises the baseline demographic and disease characteristics of the study population.

Table 11. Baseline Patient Characteristics of Evaluable Patients in Study M12-175

Characteristics	**N = 57**
Age, years; median (range)	66 (42 to 84)
White; %	91.2
Male; %	75.4
ECOG performance status[a]; % 0 1 2	 45.5 52.7 1.8
Tumor burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 35.1 66.7
Number of prior therapies; median (range)	3 (1-11)
Time since diagnosis, months; median (range)	108 (13.7-327.6)
[a]Missing for two patients.	

Among the patients, 75.4% were fludarabine refractory, 65.6% (21/32) had

~~unmutated IGHV, 30.4% (17/56) had 11q deletion, and 21.4% (12/56) had 17p del.~~

~~Overall response rate (ORR) and duration of response (DOR) were evaluated by both investigators and an IRC according to the IWCLL NCI-WG criteria. Efficacy results are shown in Table 12:~~

~~Table 12. Efficacy Results in Study M12-175~~

	~~IRC Assessment N=57~~	**~~Investigator Assessment N=57~~**
~~ORR, (%)~~ ~~(95% CI)~~	~~73.7~~ ~~(60.3, 84.5)~~	~~80.7~~ ~~(68.1, 90.0)~~
~~CR + CRi (%)~~	~~7.0~~	~~12.3~~
~~nPR (%)~~	~~0~~	~~3.5~~
~~PR (%)~~	~~66.7~~	~~64.9~~
~~DOR, % (95% CI) 12-month estimate~~	~~88.8 (67.5, 96.5)~~	~~96.6 (77.9, 99.5)~~
~~CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.~~		

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)
~~10 mg~~ Wallet containing 10 mg tablets	14 x 10 mg tablets
~~50 mg~~ Wallet containing 50 mg tablets	7 x 50 mg tablets
~~10 mg~~ Unit Dose blister containing 10 mg tablets	2 x 10 mg tablets
~~50 mg~~ Unit Dose blister containing 50 mg tablet	1 x 50 mg tablet
~~100 mg~~ Unit Dose blister containing 100 mg tablet	1 x 100 mg tablet
~~100 mg~~ 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.

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

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

החומר הפעיל 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. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם 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' ~~לונקלקסטה~~ לפני השימוש בתכשיר. יש לשמור את המדריך לעיון נוסף במידת הצורך.

התרופה מיועדת לשימוש במבוגרים מעל גיל 18.

1.למה מיועדת התרופה?

ונקלקסטה 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 קיבלו לפחות טיפול אחד לפני כן.

ונקלקסטה בשילוב עם תכשירי היפומטילציה (hypomethylating agent) או בשילוב עם ציטרבין במינון נמוך (Cytarabine) מיועדת גם לטיפול בחולים שאובחנו לראשונה עם לוקמיה מיאלואידית Acute) (myeloid leukemia [AML] חריפה, אשר אינם מתאימים לטיפול כימותרפי אינטנסיבי.

קבוצה תרפויטית: אנטינאופלסטי, מעכב BCL-2.

~~ונקלקסטה משמשת לטיפול בחולים עם:~~

- ~~לוקמיה לימפוציטית כרונית ([Chronic Lymphocytic Leukemia [CLL) או בחולים עם לימפומה של לימפוציטים קטנים ([small lymphocytic lymphoma [SLL), עם או ללא, אשר בתאי הסרטן שלהם נמצאו שינויים מסוימים ב- DNA הנקראים "מחיקה של 17p" ("17p deletion") ואשר קיבלו לפחות טיפול אחד לפני כן.~~
- ~~לוקמיה לימפוציטית כרונית ([Chronic Lymphocytic Leukemia [CLL), לאחר כישלון טיפולי בכימותרפיה ובמעכבי BCR.~~

~~לוקמיה מיאלואידית חריפה ([Acute myeloid leukemia [AML), אשר לא קיבלו טיפול קודם ושאינם מתאימים לטיפול כימותרפי אינטנסיבי. ונקלקסטה ניתנת בשילוב עם תכשירים מסוג hypomethylating- או עם מינון נמוך של ציטרבין.~~

~~CLL ו-SLL הוא הם סוגי של סרטן המשפיעים על תאי דם לבנים הנקראים "לימפוציטים" ועל בלוטות הלימפה. ב- CLL ו- SLL, לימפוציטים מתרבים מהר מדי וחיים זמן רב מדי, ולכן יש עודף תאים מסוג זה בדם.~~

~~AML הוא סרטן של תאי המקור לתאי הדם המיילואידים (תאים בלאסטים). שינויים בתאים אלה עוצרים את התפתחות התאים המיילואידים לתאי דם בוגרים. כתוצאה מכך ישנה הצטברות של התאים המיילואידים שאינם בוגרים במח העצם ובדם וכן מעט מדי תאי דם אדומים, טסיות וגרנולוציטים (סוג של תאי דם לבנים).~~

ונקלקסטה פועלת באמצעות ~~חסימה~~ 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.

~~**קבוצה תרפויטית:** אנטינאופלסטי, מעכב BCL-2.~~

2. לפני שימוש בתרופה

אין להשתמש בתרופה אם:

- אתה אלרגי לחומר הפעיל ונטוקלקס או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (מפורטים בסעיף 6).
- אתה נוטל תרופה צמחית המוכרת בשם היפריקום לטיפול בדיכאון (סנט ג'ונס וורט - St. John's wort).
- ~~אתה~~ חולה ב- CLL או SLL ונוטל תרופה אשר מעכבת אנזים CYP3A בצורה חזקה. ~~כגון התרופות נוטל אחת מהתרופות המפורטות מטה~~ **בעת התחלת הטיפול ובמהלך התקופה בה נעשית העלאה הדרגתית במינון** (בדרך כלל במשך 5 שבועות). ~~זאת~~ משום שהסיכון ללקות בתסמונת מסוכנת בשם תסמונת פירוק הגידול (tumour lysis syndrome [TLS]) יעלה ~~שתופעות חמורות ומסכנות חיים יכולות להופיע~~ כאשר נוטלים ונקלקסטה עם התרופות הללו:
  - ~~קטוקונאזול, וריקונאזול, פוסאקונאזול או איטראקונאזול לזיהומים פטרייתיים~~
  - ~~קלאריתרומיצין לזיהומים חיידקיים~~
  - ~~לופינאביר, ריטונאביר או אינדינאביר לזיהום HIV~~
  - ~~טלפרביר לטיפול בנגיף הפטיטיס C~~
- ~~קנוויופטאן לטיפול באי ספיקת לב גדשתית לא מפוצה~~

~~כאשר מינון הונקלקסטה שלך הוגדל למינון המקובל המלא, בדוק עם הרופא אם אתה יכול להתחיל לקחת תרופות אלו שוב.~~

חשוב שתספר לרופא שלך, לרוקח או לאחות על כל התרופות שאתה לוקח, כולל תרופות מרשם וללא מרשם, ויטמינים ותוספי תזונה צמחיים. ~~ייתכן שהרופא שלך יצטרך להפסיק תרופות מסוימות כאשר תתחיל לקחת ונקלקסטה לראשונה ובמשך חמשת השבועות הראשונים בהם נעשית העלאה הדרגתית במינון עד למינון המקובל המלא.~~

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

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

לפני הטיפול עם 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
- ~~יש לך בעיות בכבד מאחר ואלו עלולות לעלות את הסיכון לתופעות לוואי~~
- 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, מתכננת היריון, מניקה או מתכננת 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, ~~התכווצויות~~ פרכוסים ועלולה להוביל למוות. הסיכון ל- TLS ~~הינו~~ הוא ב-5 השבועות הראשונים לטיפול~~תחילת הטיפול – 5 השבועות 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 ורידי.
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 הווריד 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

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.

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

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 ~~התייעצי עם~~ 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 ~~עד~~ 30 יום לאחר סיום הטיפול בונקלקסטה כדי להימנע מכניסה להיריון. ~~אם את משתמשת באמצעי מניעה הורמונליים בגלולות או באביזרים/התקנים, עליך להשתמש בנוסף גם באמצעי מניעה חוצץ (כגון קונדומים) מכיוון שאמצעי מניעה הורמונליים בגלולות או באביזרים/התקנים, יכולים להיות מושפעים מונקלקסטה.~~
- ספרי לרופא מיד אם נכנסת להיריון במהלך הטיפול עם תרופה זו.

הנקה
לא ידוע אם הרכיב הפעיל בונקלקסטה עובר לחלב אם. 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.

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 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 במשך 7 ימים.
- המינון יוגדל ל- 50 מ"ג (טבליה אחת של 50 מ"ג) פעם ביום במשך 7 ימים.
- המינון יוגדל ל- 100 מ"ג (טבליה אחת של 100 מ"ג) פעם ביום במשך 7 ימים.
- המינון יוגדל ל- 200 מ"ג (שתי טבליות של 100 מ"ג) פעם ביום במשך 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.

ייתכן ותידרש התאמה של המינון בגלל תופעות לוואי או משיקולים אחרים.

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.

- 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.

- 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 ה~~חפיסה~~בליסטר:

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 ~~5 השבועות הראשונים של~~ הטיפול עם ונקלקסטה~~ ב- CLL או SLL. זה יסייע בפינוי תוצרי הפירוק של תאי סרטן מדמך, דרך השתן~~.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 תקח מנה נוספת. חזור ללוח זמני נטילת המנות הרגיל שלך למחרת.
- ~~אין לקחת מנה כפולה כדי לפצות על המנה שנשכחה.~~
- 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 בכל פעם שהנך לוקח תרופה. הרכב משקפיים אם הנך זקוק להם.

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

4. תופעות לוואי

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
- ~~כאב או נפיחות בבטן~~

ספירה נמוכה של תאי דם לבנים (נויטרופניה) (שכיחות מאוד - עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)**:** הרופא יבדוק את ספירת הדם שלך במהלך הטיפול עם ונקלקסטה. ~~ספירה נמוכה של תאי דם לבנים יכולה להגביר את הסיכון שלך לזיהום. הסימנים יכולים לכלול חום, צמרמורות, הרגשת חולשה או בלבול, שיעול, כאב או תחושת צריבה בעת מתן שתן. חלק מהזיהומים יכולים להיות חמורים ועלולים להוביל למוות.~~ספר לרופא מיד אם מופיעים אצלך סימנים של זיהום במהלך הטיפול עם ונקלקסטה.

ספר לרופא אם אתה מבחין באחת מתופעות הלוואי הבאות:

<u>בחולי CLL או SLL</u>

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
- <u>הרגשת עייפות</u>
- <u>שיעול</u>
- <u>כאבי שרירים או מפרקים</u>
- <u>נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים</u>

בנוסף, ניתן לראות בבדיקות דם
- <u>ספירה נמוכה של</u> ~~ירידה בספירת~~ תאי דם אדומים
- עלייה ברמת מלח גוף (אלקטרוליט) הנקרא זרחן
- <u>ספירה נמוכה של</u> ~~ירידה בספירת~~ טסיות
- <u>רמות גבוהות של אינזימי כבד הנקראים פוספטאזה בסיסית ([ALP] alkaline phosphatase)</u>

שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים)
- דלקת ריאות
- ~~זיהום בדרכי השתן~~
- <u>חום עם</u> ספירה נמוכה של תאי דם לבנים ~~עם חום~~(חום נויטרופני)
- <u>זיהום חמור בדם (אלח דם)</u>

בנוסף, ניתן לראות בבדיקות דם
- עלייה ברמת אוריאה
- עלייה ברמת אשלגן
- ירידה ברמת סידן
- ~~עלייה ברמות קריאטינין~~
- ספירה נמוכה של תאי דם לבנים הנקראים לימפוציטים

<u>בחולי AML</u>

<u>**שכיחות מאוד** (עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)</u>
- <u>הרגשת חולי (בחילות או הקאות)</u>
- <u>שלשול</u>
- <u>עצירות</u>
- <u>נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים</u>
- <u>הרגשת עייפות</u>
- <u>דלקת ריאות</u>

- חום עם ספירה נמוכה של תאי דם לבנים (חום נויטרופני)
- זיהום חמור בדם (אלח דם)
- פריחה
- דימום
- קוצר נשימה
- כאבי 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, וניוטרופניה או לימפופניה, באופן ספציפי)
- ספירה נמוכה של תאי דם אדומים (אנמיה)
- רמות גבוהות של סוכר בדם
- ירידה ברמות מלחי גוף (אלקטרוליט) הכוללים סידן, נתרן, אשלגן, זרחן אנאורגני או מגנזיום
- רמות נמוכות של חלבון הנקרא אלבומין
- רמות גבוהות של בילירובין כללי

שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים)

- כיחשון (Cachexia)
- 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

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, anydrous 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
<u>CLL/SLL</u> 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.
- 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.