ינואר 2024

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. מבקשת להודיע כי העלון לרופא ולצרכן של התכשירים שבנדון עודכנו.
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ההתוויות המאושרות לתכשיר:

VENCLEXTA is indicated for the treatment of:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

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

Acute Myeloid Leukemia

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

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

בברכה,

רחלי אברמוביץ'

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.**

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

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

1.2 Acute Myeloid Leukemia

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

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 (2.4) and Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

VENCLEXTA 5-week Dose Ramp-Up Schedule

Administer VENCLEXTA according to the 5-week ramp-up dosing schedule to the recommended dosage of 400 mg orally once daily as shown in Table 1.

Table 1. Dosing Schedule for 5-Week Ramp-up Phase for Patients with CLL/SLL

	VENCLEXTA Oral Daily Dose
Week 1	20 mg
Week 2	50 mg
Week 3	100 mg
Week 4	200 mg
Week 5 and beyond	400 mg

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

In Combination with Obinutuzumab

Start obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles. Refer to the obinutuzumab prescribing information for additional dosing information.

On Cycle 1 Day 22, start VENCLEXTA according to the 5-week ramp-up dosing schedule (see Table 1). After completing the ramp-up phase on Cycle 2 Day 28, continue VENCLEXTA at a dose of 400 mg orally once daily from Cycle 3 Day 1 until the last day of Cycle 12.

In Combination with Rituximab

Start rituximab administration after the patient has completed the 5-week ramp-up dosing schedule for VENCLEXTA (see Table 1) and has received VENCLEXTA at the recommended dosage of 400 mg orally once daily for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, at a dose of 375 mg/m^2 intravenously for Cycle 1 and 500 mg/m^2 intravenously for Cycles 2-6. Continue VENCLEXTA 400 mg orally once daily for 24 months from Cycle 1 Day 1 of rituximab.

Refer to the rituximab prescribing information for additional dosing information.

Monotherapy

The recommended dosage of VENCLEXTA is 400 mg once daily after completion of the 5-week ramp-up dosing schedule (see Table 1). Continue VENCLEXTA until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for Acute Myeloid Leukemia

The recommended dosage and ramp-up of VENCLEXTA depends upon the combination agent. ~~The VENCLEXTA~~Follow the dosing schedule, ~~(~~including the 3-day or 4-day dose ramp-up~~),~~ ~~i~~as shown in Table 2. ~~Initiate the azacitidine or decitabine or low-dose cytarabine on Day 1.~~ Start VENCLEXTA administration on Cycle 1 Day 1 in combination with:

Azacitidine 75 mg/m^2 intravenously or subcutaneously once daily on Days 1-7 of each 28-day cycle; OR

Decitabine 20 mg/m^2 intravenously once daily on Days 1-5 of each 28-day cycle; OR

Cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle.

Table 2. Dosing Schedule for 3- or 4-Day Ramp-up Phase in Patients with AML

	VENCLEXTA Oral Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg orally once daily of each 28-day cycle ~~when dosing~~ in combination with **azacitidine or decitabine**	600 mg orally once daily of each 28-day cycle ~~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.

Refer to *Clinical Studies (14.2)* and Prescribing Information for azacitidine, decitabine, or cytarabine for additional dosing information.

2.4 Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

Patients treated with VENCLEXTA may develop tumor lysis syndrome (TLS). Refer to the appropriate section below for specific details on management. Assess patient-specific factors for level of risk of 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. TLS can also occur upon resumption of VENCLEXTA following a dosage interruption. See Table 4 and Table 5 for dose modifications of VENCLEXTA after interruption.

The risk of TLS is a continuum based on multiple factors, particularly reduced renal function (creatinine clearance [CLcr] <80 mL/min) and tumor burden; splenomegaly may also increase the risk of TLS.

Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA. The risk may decrease as tumor burden decreases *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

Table 3 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumor burden determination from clinical trial data. Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule. Reassess the risk of TLS when reinitiating VENCLEXTA after a dosage interruption lasting more than 1 week during the ramp-up phase, or more than 2 weeks after completion of ramp-up. Institute prophylaxis and monitoring as needed.

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

Tumor Burden	**Prophylaxis**		**Blood Chemistry Monitoring[c,d]**
	Hydration[a]	**Anti-hyperuricemics[b]**	**Setting and Frequency of Assessments**

Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5 to 2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5 to 2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CLcr<80ml/min ; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5 to 2L) and intravenous (150 to 200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

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

Acute Myeloid Leukemia

- All patients should have white blood cell count less than 25×10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required.
- Prior to first VENCLEXTA dose, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents and continue during ramp-up phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function), consider additional measures, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

2.5 Dosage Modifications for Adverse Reactions~~Based on Toxicities~~

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

~~Interrupt dosing or reduce dose for toxicities. See Table 4 and Table 5 for~~ The recommended ~~dose~~ dosage modifications for ~~toxicities related to~~ VENCLEXTA~~.~~ for adverse reactions are provided in Table 4 and the recommended dose reductions for VENCLEXTA for adverse reactions are provided in Table 5.

For patients having a dosage interruption lasting more than 1 week during the ramp-up phase, or more than 2 weeks after completion of ramp-up, 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.~~2~~4)]*.

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

Adverse Reaction~~Event~~	Occurrence	Dosage Modification~~Action~~
Tumor Lysis Syndrome		

Blood chemistry changes or symptoms suggestive of TLS *[see Warnings and Precautions (5.1)]*	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at ~~the~~ same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at ~~a~~ reduced dose (see Table 5) ~~*[see Dosage and Administration (2.2)]*~~.
		For any events of clinical TLS,[b] resume at ~~a~~ reduced dose following resolution (see Table 5) ~~*[see Dosage and Administration (2.2)]*~~.
Non-Hematologic Adverse Reactions~~Toxicities~~		
Grade 3 or 4 non-hematologic toxicities *[see Adverse Reactions (6.1)]*	1st occurrence	Interrupt VENCLEXTA. ~~Once the toxicity has resolved~~ Upon resolution to Grade 1 or baseline level, resume VENCLEXTA ~~therapy may be resumed~~ at the same dose. ~~No dose modification is required.~~
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Adverse Reactions~~Toxicities~~		
Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	Interrupt VENCLEXTA. ~~To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved~~ Upon resolution to Grade 1 or baseline level, resume VENCLEXTA ~~therapy may be resumed~~ at the same dose.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. ~~Consider using G-CSF as clinically indicated.~~ Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for		

more than 2 weeks.
[a]Adverse reactions were graded using NCI CTCAE version 4.0.
[b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures *[see Adverse Reactions (6.1)]*.

Table 5. Recommended Dose Reduction for ~~Toxicity During~~ Adverse Reactions for VENCLEXTA ~~Treatment~~ in CLL/SLL

Dose at Interruption, mg	Restart Dose, mg[a,b]
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.
[b]If a dosage interruption lasts more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up, reassess the risk of TLS and determine if reinitiation at a reduced dosage is necessary *[see Dosage and Administration (2.2, 2.4)]*.

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 (6.1)]* may require dose~~ Dose modification and interruptions ~~or permanent discontinuation~~ for cytopenias are dependent on remission status. Dose modifications of VENCLEXTA. ~~Table 6 shows the dose modification guidelines for hematologic toxicities.~~ for adverse reactions are provided in Table 6.

Table 6. Recommended ~~Dose~~ VENCLEXTA Dosage Modifications for ~~Toxicities[a]~~ Adverse Reactions in AML

Adverse Reaction~~Event~~	Occurrence	Dosage Modification~~Action~~
Hematologic Adverse Reactions~~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[a]	~~Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated.~~ In most instances, do not interrupt VENCLEXTA ~~and~~ in combination with azacitidine, decitabine, or low-dose cytarabine ~~cycles should not be~~

Adverse Reaction~~Event~~	Occurrence	Dosage Modification~~Action~~
		~~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~~ in combination with 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~~ Upon resolution 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~~ in combination with azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts. ~~Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved~~ Upon resolution to Grade 1 or 2, resume VENCLEXTA ~~therapy~~ at the same dose ~~and the~~ in combination with azacitidine, decitabine, or low-dose cytarabine, and reduce VENCLEXTA duration ~~reduced~~ by 7 days ~~for~~ during each of the subsequent cycles, such as 21 days instead of 28 days ~~cycle~~.
~~[a]Adverse reactions were graded using NCI CTCAE version 4.0.~~ **Non-Hematologic Adverse Reactions**		
Grade 3 or 4 non-hematologic toxicities *[see Adverse Reactions (6.1)]*	Any occurrence	Interrupt VENCLEXTA if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.
[a] Recommend bone marrow evaluation.		

2.6 Dosage Modifications for Drug Interactions

Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

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

Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see ~~Dosage and Administration (2.3) and~~ Drug Interactions (7.1)]*.

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

<table>
<tr><th>Coadministered Drug</th><th colspan="2">Initiation and Ramp-Up Phase</th><th>Steady Daily Dose (After Ramp-Up Phase) [a]</th></tr>
<tr><td rowspan="2">Posaconazole</td><td>CLL/SLL</td><td>Contraindicated</td><td rowspan="2">Reduce VENCLEXTA dose to 70 mg.</td></tr>
<tr><td>AML</td><td>Day 1 – 10 mg
Day 2 – 20 mg
Day 3 – 50 mg
Day 4 – 70 mg</td></tr>
<tr><td rowspan="2">Other strong CYP3A inhibitor</td><td>CLL/SLL</td><td>Contraindicated</td><td rowspan="2">Reduce VENCLEXTA dose to 100 mg.</td></tr>
<tr><td>AML</td><td>Day 1 – 10 mg
Day 2 – 20 mg
Day 3 – 50 mg
Day 4 – 100 mg</td></tr>
<tr><td>Moderate CYP3A inhibitor</td><td colspan="3" rowspan="2">Reduce the VENCLEXTA dose by at least 50%.</td></tr>
<tr><td>P-gp inhibitor</td></tr>
<tr><td colspan="4">[a]In patients with CLL/SLL, consider alternative medications or reduce the VENCLEXTA dose as described in Table 7.</td></tr>
</table>

2.7 Dosage Modifications for Patients with Severe Hepatic Impairment

Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions *[see Use in Specific Populations (8.7)]*.

2.8 Administration

Instruct patients of the following:

- Take VENCLEXTA with a meal and water.
- Take VENCLEXTA at approximately the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break tablets prior to swallowing.

The recommended dosage of VENCLEXTA may be delivered using any of the approved tablet strengths (e.g., patients can take 2 x 50 mg tablets or 10 x 10 mg tablets instead of 1 x 100 mg tablet as needed).

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, instruct the patient to 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, instruct the patient not to take the missed dose and resume the usual dosing schedule the next day.

If the patient vomits following dosing, instruct the patient to not take an additional dose that day and to take the next prescribed dose at the usual time.

3 DOSAGE FORMS AND STRENGTHS

Table 8. VENCLEXTA Tablet Strength and Description

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

4 CONTRAINDICATIONS

Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome *[see Dosage and Administration (2.6) and Drug Interactions (7.1)]*.

Concomitant use of preparations containing St. John’s wort

Hypersensitivity to the active substance venetoclax, or to any of the excipients listed in section 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 treated with VENCLEXTA *[see Adverse Reactions (6.1)]*. VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase. TLS, including fatal cases, has been reported after a single 20 mg dose of VENCLEXTA.

In patients with CLL/SLL who followed the current (5-week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL/SLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3- week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure *[see Adverse Reactions (6.1)]*.

In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine (VIALE-A). In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine (VIALE-C) *[see Adverse Reactions (6.1)]*.

The risk of TLS is a continuum based on multiple factors, particularly reduced renal function , tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.

Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases Interrupt dosing if needed; when restarting VENCLEXTA, follow dose modification guidance *[see Dosage and Administration (2.1, 2.2, 2.3,2.4) and Use in Specific Populations (8.6)]*.

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase of VENCLEXTA. For patients with CLL/SLL, coadministration of VENCLEXTA with strong CYP3A inhibitors at initiation and during the 5-week ramp-up phase is contraindicated *[see Contraindications (4)]*. For patients with AML, reduce the dose of VENCLEXTA when coadministered with strong CYP3A inhibitors at initiation and during the 3- or 4-day ramp-up phase. For patients with CLL/SLL or AML, reduce the dose of VENCLEXTA when coadministered with moderate CYP3A4 inhibitors or P-gp inhibitors *[see Dosage and Administration (2.6) and Drug Interactions (7.1)]*.

5.2 Neutropenia

In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with VENCLEXTA in

combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients *[see Adverse Reactions (6.1)]*.

In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine. Neutropenia can recur with subsequent cycles.

Monitor complete blood counts throughout the treatment period. For interruption and dose resumption of VENCLEXTA for severe neutropenia, see Table 4 for CLL and Table 6 for AML *[see Dosage and Administration (2.5)]*. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF) ~~*[see Dosage and Administration (2.3)]*~~.

5.3 Infections

Fatal and serious infections, such as pneumonia and sepsis, have occurred in patients treated with VENCLEXTA *[see Adverse Reactions (6.1)]*.

Monitor patients ~~closely~~ for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 ~~higher~~ infection until resolution. For dose resumptions, see Table 4 for CLL and Table 6 for AML *[see Dosage and Administration (2.5)]*.

5.4 Immunization

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

5.5 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at a dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.6 Effects on ability to drive and use machines

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Tumor Lysis Syndrome *[see Warnings and Precautions (5.1)]*

- Neutropenia *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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.

In CLL/SLL, the safety population reflects exposure to VENCLEXTA as monotherapy in patients in M13-982, M14-032, and M12-175 and in combination with obinutuzumab or rituximab in patients in CLL14 and MURANO. In this CLL/SLL safety population, the most common adverse reactions (≥20%) for VENCLEXTA were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

In AML, the safety population reflects exposure to VENCLEXTA in combination with decitabine, azacitidine, or low-dose cytarabine in patients in M14-358, VIALE-A, and VIALE-C. In this safety population, the most common adverse reactions (⩾30% in any trial) were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA in Combination with Obinutuzumab

The safety of VENCLEXTA in combination with obinutuzumab (VEN+G) (N=212) versus obinutuzumab in combination with chlorambucil (GClb) (N=214) was evaluated in CLL14, a randomized, open-label, actively controlled trial in patients with previously untreated CLL *[see Clinical Studies (14.1)]*. Patients randomized to the VEN+G arm were treated with VENCLEXTA and obinutuzumab in combination for six cycles, then with VENCLEXTA as monotherapy for an additional six cycles. Patients initiated the first dose of the 5-week ramp-up for VENCLEXTA on Day 22 of Cycle 1 and once completed, continued VENCLEXTA 400 mg orally once daily for a total of 12 cycles. The trial required a total Cumulative Illness Rating Scale (CIRS) >6 or CLcr <70 mL/min, hepatic transaminases and total bilirubin ≤2 times upper limit of normal and excluded patients with any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system. The median duration of exposure to VENCLEXTA was 10.5 months (range: 0 to 13.5 months) and the median number of cycles of obinutuzumab was 6 in the VEN+G arm.

Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.

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

Table 9 presents adverse reactions identified in CLL14.

Table 9. Adverse Reactions (≥10%) in Patients Treated with VEN+G in CLL14

Adverse Reaction	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	60	56	62	52
Anemia[a]	17	8	20	7
Gastrointestinal disorders				
Diarrhea	28	4	15	1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				
Fatigue[a]	21	2	23	1
Infections and infestations				
Upper respiratory tract infection[a]	17	1	17	1
[a]Includes multiple adverse reaction terms.				

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

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

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

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

During treatment with VENCLEXTA monotherapy after completion of VEN+G, the adverse reaction that occurred in ≥10% of patients was neutropenia (26%). The grade ≥3 adverse reactions that occurred in ≥2% of patients were neutropenia (23%) and anemia (2%).

Table 10 presents laboratory abnormalities CLL14.

Table 10. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+G in CLL14

Laboratory Abnormality[a]	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukopenia	90	46	89	41

Laboratory Abnormality[a]	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Lymphopenia	87	57	87	51
Neutropenia	83	63	79	56
Thrombocytopenia	68	28	71	26
Anemia	53	15	46	11
Chemistry				
Blood creatinine increased	80	6	74	2
Hypocalcemia	67	9	58	4
Hyperkalemia	41	4	35	3
Hyperuricemia	38	38	38	38
[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

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

VENCLEXTA in Combination with Rituximab

The safety of VENCLEXTA in combination with rituximab (VEN+R) (N=194) versus bendamustine in combination with rituximab (B+R) (N=188) was evaluated in MURANO *[see Clinical Studies (14.1)]*. 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 VENCLEXTA monotherapy, for a total of 24 months after ramp-up. At the time of analysis, the median duration of exposure to VENCLEXTA was 22 months and the median number of cycles of rituximab was 6 in the VEN+R arm.

Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with most frequent (≥5%) being pneumonia (9%). 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.

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

Table 11 presents adverse reactions identified in MURANO.

Table 11. Adverse Reactions (≥10%) in Patients Treated with VEN+R in MURANO

Adverse Reaction	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades (%)	Grade ⩾ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	65	62	50	44
Anemia[a]	16	11	23	14
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Nausea	21	1	34	1
Constipation	14	<1	21	0
Infections and infestations				
Upper respiratory tract infection[a]	39	2	23	2
Lower respiratory tract infection[a]	18	2	10	2
Pneumonia[a]	10	7	14	10
General disorders and administration site conditions				
Fatigue[a]	22	2	26	<1
[a]Includes multiple adverse reaction terms.				

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

Blood and lymphatic system disorders: febrile neutropenia (4%)

Gastrointestinal disorders: vomiting (8%)

Infections and infestations: sepsis (<1%)

Metabolism and nutrition disorders: tumor lysis syndrome (3%)

During treatment with VENCLEXTA monotherapy after completion of VEN+R combination treatment, adverse reactions that occurred in ≥10% of patients were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infections (11%). The Grade 3 or 4 adverse reactions that occurred in ≥2% of patients were neutropenia (12%) and anemia (3%).

Table 12 presents laboratory abnormalities identified in MURANO.

Table 12. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+R in MURANO

Laboratory Abnormality	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	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
Anemia	50	12	63	15
Thrombocytopenia	49	15	60	20
Chemistry				
Blood creatinine increased	77	<1	78	1
Hypocalcemia	62	5	51	2
Hyperuricemia	36	36	33	33
Hyperkalemia	24	3	19	2

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

Grade 4 laboratory abnormalities that developed 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%).

VENCLEXTA as Monotherapy

The safety of VENCLEXTA was evaluated in pooled data from three single-arm trials (M13-982, M14-032, and M12-175). Patients received VENCLEXTA 400 mg orally once daily after completing the ramp-up phase (N= 352). The median duration of treatment with VENCLEXTA at the time of data analysis was 14.5 months (range: 0 to 50 months). Fifty-two percent of patients received VENCLEXTA for more than 60 weeks.

In the pooled dataset, the median age was 66 years (range: 28 to 85 years), 93% were White, and 68% were male. The median number of prior therapies was 3 (range: 0 to 15).

Serious adverse reactions were reported in 52% of patients, with the most frequent (≥5%) being pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

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

Table 13 presents adverse reactions identified in these trials.

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

Adverse Reaction	VENCLEXTA (N = 352)	
	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders		
Neutropenia[a]	50	45
Anemia[a]	33	18
Thrombocytopenia[a]	29	20
Lymphopenia[a]	11	7
Febrile neutropenia	6	6
Gastrointestinal disorders		
Diarrhea	43	3
Nausea	42	1
Abdominal pain[a]	18	3
Vomiting	16	1
Constipation	16	<1
Mucositis[a]	13	<1
Infections and infestations		
Upper respiratory tract infection[a]	36	1
Pneumonia[a]	14	8
Lower respiratory tract infection[a]	11	2
General disorders and administration site conditions		
Fatigue[a]	32	4
Edema[a]	22	2
Pyrexia	18	<1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[a]	29	2
Arthralgia	12	<1
Respiratory, thoracic, and mediastinal disorders		
Cough[a]	22	0
Dyspnea[a]	13	1
Nervous system disorders		
Headache	18	<1
Dizziness[a]	14	0
Skin and subcutaneous tissue disorders		
Rash[a]	18	<1
Adverse reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.		

Adverse Reaction	VENCLEXTA (N = 352)	
	All Grades (%)	Grade ≥3 (%)
[a]Includes multiple adverse reaction terms.		

Table 14 presents 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 14. New or Worsening Laboratory Abnormalities in ≥40% (All Grades) or ≥10% (Grade 3 or 4) of Patients with Previously Treated CLL/SLL Who Received VENCLEXTA Monotherapy

Laboratory Abnormality	VENCLEXTA (N = 352)	
	All Grades[a] (%)	Grade 3 or 4 (%)
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 in CLL/SLL

Tumor Lysis Syndrome

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

CLL14

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

MURANO

The incidence of TLS was 3% (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in sections 2.*2* and 2.*4 [see Dosage and Administration (2.2, 2.4)]*. 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 *[see Dosage and Administration (2.2, 2.4)]*. Rates of laboratory abnormalities relevant to TLS for patients treated with VEN+R are presented in Table 12.

Monotherapy Studies (M13-982 and M14-032)

In 168 patients with CLL treated according to recommendations described in sections 2.1 and 2.2, the rate of TLS was 2% *[see Dosage and Administration (2.2, 2.4)]*. 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 absolute lymphocyte count (ALC) ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures was observed in these patients. All patients had CLcr ≥50 mL/min. Laboratory abnormalities relevant to TLS were hyperkalemia (17% all Grades, 1% Grade ≥3), hyperphosphatemia (14% all Grades, 2% Grade ≥3), hypocalcemia (16% all Grades, 2% Grade ≥3), and hyperuricemia (10% all Grades, <1% Grade ≥3).

In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting doses, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. After this experience, TLS risk assessment, dosing regimen, TLS prophylaxis and monitoring measures were revised *[see Dosage and Administration (2.2, 2.4)]*.

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

The safety of VENCLEXTA in combination with azacitidine (VEN+AZA) (N=283) versus placebo in combination with azacitidine (PBO+AZA) (N=144) was evaluated in VIALE-A, a double-blind, randomized trial, in patients with newly diagnosed AML *[see Clinical Studies (14.2)]*. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr < 45 mL/min, or other comorbidity. Patients were randomized to receive VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or placebo in combination with azacitidine. Among patients who received VEN+AZA, the median duration of exposure to VENCLEXTA was 7.6 months (range: <0.1 to 30.7 months).

Serious adverse reactions were reported in 83% of patients who received VEN+AZA, with the most frequent (≥5%) being febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). Fatal adverse reactions occurred in 23% of patients who received VEN+AZA, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 24% of patients, dose reductions in 2%, and dose interruptions in 72%. Adverse reactions which led to discontinuation of VENCLEXTA in ≥2% of patients were sepsis (excluding fungal; 3%) and pneumonia (2%). The most frequent adverse reaction leading to dose reduction was pneumonia (0.7%). Adverse reactions which required a dose interruption in ≥5% of patients included febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), sepsis (excluding fungal; 11%), and thrombocytopenia (10%). Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for absolute neutrophil count (ANC) <500/microliter.

Table 15 presents adverse reactions identified in VIALE-A.

Table 15. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	44	2	35	<1
Diarrhea[a]	43	5	33	3
Vomiting[b]	30	2	23	<1
Stomatitis[c]	18	1	13	0
Abdominal pain[d]	18	<1	13	0
Blood and lymphatic system disorders				
Febrile neutropenia	42	42	19	19
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[e]	36	2	28	1
General disorders and administration site conditions				
Fatigue[f]	31	6	23	2
Edema[g]	27	<1	19	0
Vascular disorders				
Hemorrhage[h]	27	7	24	3
Hypotension[i]	12	5	8	3
Metabolism and nutrition disorders				
Decreased appetite[j]	25	4	17	<1
Skin and subcutaneous tissue disorders				

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Rash[k]	25	1	15	0
Infections and infestations				
Sepsis[l] (excluding fungal)	22	22	16	14
Urinary tract infection[m]	16	6	9	6
Respiratory, thoracic and mediastinal disorders				
Dyspnea[n]	18	4	10	2
Nervous system disorders				
Dizziness[o]	17	<1	8	<1

[a]Includes diarrhea and colitis.
[b]Includes vomiting and hematemesis.
[c]Includes stomatitis, mouth ulceration, mucosal inflammation, cheilitis, aphthous ulcer, glossitis, and tongue ulceration.
[d]Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.
[e]Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, bone pain, myalgia, neck pain, non-cardiac chest pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, spinal pain, and musculoskeletal discomfort.
[f]Includes fatigue and asthenia.
[g]Includes edema peripheral, edema, generalized edema, eyelid edema, face edema, penile edema, periorbital edema, and swelling.
[h]Includes epistaxis, hematuria, conjunctival hemorrhage, hemoptysis, hemorrhoidal hemorrhage, gingival bleeding, mouth hemorrhage, hemorrhage intracranial, vaginal hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, muscle hemorrhage, skin hemorrhage, upper gastrointestinal hemorrhage, anal hemorrhage, eye hemorrhage, gastritis hemorrhagic, hemorrhage, hemorrhage urinary tract, hemorrhagic diathesis, hemorrhagic stroke, hemorrhagic vasculitis, lower gastrointestinal hemorrhage, mucosal hemorrhage, penile hemorrhage, post procedural hemorrhage, rectal hemorrhage, retinal hemorrhage, shock hemorrhagic, soft tissue hemorrhage, subdural hemorrhage, tongue hemorrhage, urethral hemorrhage, vessel puncture site hemorrhage, vitreous hemorrhage and wound hemorrhage.
[i]Includes hypotension and orthostatic hypotension.
[j]Includes decreased appetite and hypophagia.
[k]Includes rash, rash maculo-papular, rash macular, drug eruption, rash papular, rash pustular, eczema, rash erythematous, rash pruritic, dermatitis acneiform, rash morbilliform, dermatitis, eczema asteatotic, exfoliative rash, and perivascular dermatitis.
[l]Includes sepsis, escherichia bacteremia, escherichia sepsis, septic shock, bacteremia, staphylococcal bacteremia, klebsiella bacteremia, staphylococcal sepsis, streptococcal bacteremia, enterococcal bacteremia, klebsiella sepsis, pseudomonal bacteremia, pseudomonal sepsis, urosepsis, bacterial sepsis, clostridial sepsis, enterococcal sepsis, neutropenic sepsis, and streptococcal sepsis.

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
[m]Includes urinary tract infection, escherichia urinary tract infection, cystitis, urinary tract infection enterococcal, urinary tract infection bacterial, pyelonephritis acute, and urinary tract infection pseudomonal. [n]Includes dyspnea, dyspnea exertional, and dyspnea at rest. [o]Includes dizziness and vertigo.				

Other clinically important adverse reactions (All Grades) at ⩾10% that did not meet criteria for Table 15 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (4%)

Infections and infestations: pneumonia[b] (33%)

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

Nervous system disorders: headache[c] (11%)

Investigations: weight decreased (13%).

[a]Includes cholecystitis acute, cholelithiasis, cholecystitis, and cholecystitis chronic.

[b]Includes pneumonia, lung infection, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, lower respiratory tract infection, pneumonia viral, lower respiratory tract infection fungal, pneumonia hemophilus, pneumonia pneumococcal, and pneumonia respiratory syncytial viral.

[c]Includes headache and tension headache.

Table 16 presents laboratory abnormalities identified in VIALE-A.

Table 16. New or Worsening Laboratory Abnormalities (⩾10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ⩾5% for All Grades or ⩾ 2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Laboratory Abnormality	VENCLEXTA + Azacitidine		Placebo + Azacitidine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	98	98	88	81
Platelet decreased	94	88	94	80
Lymphocytes decreased	91	71	72	39
Hemoglobin decreased	61	57	56	52
Chemistry				
Bilirubin increased	53	7	40	4
Calcium decreased	51	6	39	9
Sodium decreased	46	14	47	8

Laboratory Abnormality	VENCLEXTA + Azacitidine		Placebo + Azacitidine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Alkaline phosphatase increased	42	1	29	<1
Blood bicarbonate decreased	31	<1	25	0
The denominator used to calculate the rate varied from 85 to 144 in the PBO+AZA arm and from 125 to 283 in the VEN+AZA arm based on the number of patients with at least one post-treatment value.				

VENCLEXTA in Combination with Azacitidine or Decitabine

The safety of VENCLEXTA in combination with azacitidine (N=67) or decitabine (N=13) was evaluated in M14-358, a non-randomized trial of patients with newly diagnosed AML. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity *[see Clinical Studies (14.2)]*. Patients received VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or decitabine (20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle).

Azacitidine

The median duration of exposure to VENCLEXTA when administered in combination with azacitidine was 6.5 months (range: 0.1 to 38.1 months). The safety of VENCLEXTA in combination with azacitidine in this trial is consistent with that of VIALE-A.

Decitabine

The median duration of exposure to VENCLEXTA when administered in combination with decitabine was 8.4 months (range: 0.5 to 39 months).

Serious adverse reactions were reported in 85% of patients who received VENCLEXTA with decitabine, the most frequent (≥10%) being sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Permanent discontinuation of VENCLEXTA due to adverse reactions occurred in 38% of patients. The most frequent adverse reaction leading to permanent discontinuation (≥5%) was pneumonia (8%).

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

Dosage interruptions of VENCLEXTA due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions leading to dose interruption (≥ 10%) were neutropenia (38%), febrile neutropenia (23%), leukopenia (15%), and pneumonia (15%).

The most common adverse reactions (≥30%) were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal

pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). The most common laboratory abnormalities (≥30%) were neutrophils decreased (100%), lymphocytes decreased (100%), white blood cells decreased (100%), platelets decreased (92%), calcium decreased (85%), hemoglobin decreased (69%), glucose increased (69%), magnesium decreased (54%), potassium decreased (46%), bilirubin increased (46%), albumin decreased (38%), alkaline phosphatase increased (38%), sodium decreased (38%), ALT increased (31%), creatinine increased (31%), and potassium increased (31%).

VENCLEXTA in Combination with Low-Dose Cytarabine

VIALE-C

The safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) (N=142) versus placebo with low-dose cytarabine (PBO+LDAC) (N=68) was evaluated in VIALE-C, a double-blind randomized trial in patients with newly diagnosed AML. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity *[see Clinical Studies (14.2)]*. Patients were randomized to receive VENCLEXTA 600 mg orally once daily after completion of a 4-day ramp-up phase in combination with low-dose cytarabine (20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle) or placebo in combination with low-dose cytarabine. Among patients who received VEN+LDAC, the median duration of exposure to VENCLEXTA was 3.9 months (range: <0.1 to 17.1 months).
Serious adverse reactions were reported in 65% of patients who received VEN+LDAC, with the most frequent (≥10%) being pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). Fatal adverse reactions occurred in 23% of patients who received VEN+LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 25% of patients, dose reductions in 9%, and dose interruptions in 63%. The most frequent adverse reaction (>2%) which resulted in permanent discontinuation of VENCLEXTA was pneumonia (6%). Adverse reactions which required a dose reduction in ≥1% of patients were pneumonia (1%) and thrombocytopenia (1%), and the adverse reactions which required a dose interruption in ≥5% of patients included neutropenia (20%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (6%), and sepsis (excluding fungal; 6%). Among patients who achieved bone marrow clearance of leukemia, 32% underwent dose interruptions for ANC <500/microliter.

Table 17 presents adverse reactions identified in VIALE-C.

Table 17. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+LDAC with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Compared with PBO+LDAC in VIALE-C

Adverse Reaction	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	42	1	31	0
Diarrhea	28	3	16	0
Vomiting	25	<1	13	0
Abdominal pain[a]	15	<1	9	3
Stomatitis[b]	15	1	6	0
Blood and lymphatic system disorders				
Febrile neutropenia	32	32	29	29
Infections and infestations				
Pneumonia[c]	29	19	21	21
Vascular Disorders				
Hemorrhage[d]	27	8	16	1
Hypotension[e]	11	5	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	23	3	18	0
General Disorders and Administration Site Conditions				
Fatigue[g]	22	2	21	0
Nervous System Disorders				
Headache	11	0	6	0

[a]Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.
[b]Includes stomatitis, mouth ulceration, aphthous ulcer, glossitis, mucosal inflammation, and tongue ulceration.
[c]Includes pneumonia, lung infection, lower respiratory tract infection, pneumonia fungal, lower respiratory tract infection fungal, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia cytomegaloviral, and pneumonia pseudomonal.
[d]Includes epistaxis, conjunctival hemorrhage, hemoptysis, gastrointestinal hemorrhage, gingival bleeding, mouth hemorrhage, upper gastrointestinal hemorrhage, hematuria, retinal hemorrhage, catheter site hemorrhage, cerebral hemorrhage, gastric hemorrhage, gastritis hemorrhagic, hemorrhage intracranial, hemorrhage subcutaneous, lip hemorrhage, mucosal hemorrhage, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary alveolar hemorrhage, pulmonary hemorrhage, tooth pulp hemorrhage, uterine hemorrhage, and vascular access site hemorrhage.
[e]Includes hypotension and orthostatic hypotension.

Adverse Reaction	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
[f]Includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, arthritis, bone pain, musculoskeletal chest pain, and spinal pain. [g]Includes fatigue and asthenia.				

Other clinically important adverse reactions (All Grades) at ⩾10% that did not meet criteria for Table 17 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (1%)

Infections and infestations: sepsis[b] (excluding fungal; 15%), urinary tract infection[c] (8%)

Metabolism and nutrition disorders: decreased appetite (19%), tumor lysis syndrome (6%)

Nervous system disorders: dizziness[d] (9%)

Respiratory, thoracic, and mediastinal disorders: dyspnea[e] (10%)

Investigations: weight decreased (9%).

[a]Includes cholecystitis and cholecystitis acute

[b]Includes sepsis, bacteremia, septic shock, neutropenic sepsis, staphylococcal bacteremia, streptococcal bacteremia, bacterial sepsis, Escherichia bacteremia, pseudomonal bacteremia, and staphylococcal sepsis

[c]Includes urinary tract infection and escherichia urinary tract infection

[d]Includes dizziness and vertigo

[e]Includes dyspnea and dyspnea exertional.

Table 18 describes laboratory abnormalities identified in VIALE-C.

Table 18. New or Worsening Laboratory Abnormalities (⩾10%) in Patients with AML Who Received VEN+LDAC with Difference Between Arms of ⩾5% for All Grades or ⩾ 2% for Grade 3 or 4 Reactions Compared with PBO+LDAC in VIALE-C

Laboratory Abnormality	VENCLEXTA + Low-Dose Cytarabine		Placebo + Low-Dose Cytarabine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Platelets decreased	97	95	92	90
Neutrophils decreased	95	92	82	71
Lymphocytes decreased	92	69	65	24
Hemoglobin decreased	63	57	57	54
Chemistry				
Bilirubin increased	61	7	38	7

Laboratory Abnormality	VENCLEXTA + Low-Dose Cytarabine		Placebo + Low-Dose Cytarabine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Albumin decreased	61	6	43	4
Potassium decreased	56	16	42	14
Calcium decreased	53	8	45	13
Glucose increased	52	13	59	9
AST increased	36	6	37	1
Alkaline phosphatase increased	34	1	26	1
ALT increased	30	4	26	1
Sodium increased	11	3	6	1
The denominator used to calculate the rate varied from 38 to 68 in the PBO+LDAC arm and from 65 to 142 in the VEN+LDAC arm based on the number of patients with at least one post-treatment value.				

M14-387

The safety of VENCLEXTA in combination with low-dose cytarabine (N=61) was evaluated in M14-387, a non-randomized, open- label trial of patients with newly diagnosed AML *[see Clinical Studies (14.2)]*. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients received VENCLEXTA 600 mg orally once daily after completion of the ramp-up phase in combination with low-dose cytarabine (20mg/m^2 subcutaneously on Days 1-10 of each 28-day cycle). The safety of VENCLEXTA in combination with low-dose cytarabine is consistent with that of VIALE-C.

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

https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VENCLEXTA

Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax C_{max} and $AUC_{0\text{-}INF}$ *[see Clinical Pharmacology (12.3*)], which may increase VENCLEXTA toxicities, including the risk of TLS *[see Warnings and Precautions (5.1)]*.

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 monitor more frequently for adverse reactions *[see Dosage and Administration (2.5, 2.6)]*.

In patients with AML, adjust VENCLEXTA dosage and monitor more frequently for adverse reactions *[see Dosage and Administration (2.5, 2.6)]*.

Resume the VENCLEXTA dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.5*, *2.6)]*.

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

Strong or Moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases venetoclax C_{max} and $AUC_{0\text{-}INF}$ *[see Clinical Pharmacology (12.3)]*, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see *Contraindications (4)*)

7.2 Effect of VENCLEXTA on Other Drugs

Warfarin

Concomitant use of VENCLEXTA increases warfarin C_{max} and $AUC_{0\text{-}INF}$ *[see Clinical Pharmacology (12.3)]*, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA.

P-gp Substrates

Concomitant use of VENCLEXTA increases C_{max} and $AUC_{0\text{-}INF}$ 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

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. There are no available data on VENCLEXTA use in pregnant women to inform a drug-associated risk. Administration of venetoclax to pregnant mice during the period of organogenesis was fetotoxic at exposures 1.2 times the human exposure at the recommended dose of 400 mg daily based on AUC. Advise pregnant women 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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 exposure at the recommended dose of 400 mg once 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 or the effects on the breastfed child or milk production. Venetoclax was present in the milk when administered to lactating rats *(see Data)*.

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Data

Animal Data

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8 to 10 days post-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 when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating VENCLEXTA.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose.

Infertility

Based on findings in animals, VENCLEXTA may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of VENCLEXTA have not been established in pediatric patients.

Juvenile Animal Toxicity Data

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

8.5 Geriatric Use

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Of the 352 patients with previously treated CLL/SLL evaluated for safety from 3 open-label trials of VENCLEXTA monotherapy, 57% (201/352) were ≥65 years of age and 18% (62/352) were ≥75 years of age. No clinically meaningful differences in safety and effectiveness were observed between older and younger patients in the combination and monotherapy studies.

Acute Myeloid Leukemia

Of the 283 patients who received VENCLEXTA with azacitidine in VIALE-A, 96% were ⩾65 years of age and 60% were ⩾75 years of age.

Of the 13 patients who received VENCLEXTA in combination with decitabine in M14-358, 100% were ⩾65 years of age and 62% were ⩾75 years of age.

Of the 142 patients who received VENCLEXTA in combination with low-dose cytarabine in VIALE-C, 92% were ⩾65 years of age and 57% were ⩾75 years of age. Clinical studies of VENCLEXTA in patients with AML did not include sufficient numbers of younger adults to determine if patients 65 years of age and older respond differently from younger adults.

8.6 Renal Impairment

Patients with reduced renal function (CrCl<80ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase *[see Dosage and Administration (2.1,2.2, 2.3,2.4) and Warnings and Precautions (5.1)]*. Venetoclax

should be administered to patients with severe renal impairment (CrCl≥15ml/min and <30ml/min) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS [*see Warnings and Precautions (5.1)*].

No dose adjustment is needed for patients with mild, moderate or severe renal impairment (CrCl≥15ml/min and <90ml/min) [*see Clinical Pharmacology (12.3)]*.

~~Due to the increased risk of TLS, patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA *[see Dosage and Administration (2.1,2.2, 2.3,2.4) 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.~~

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

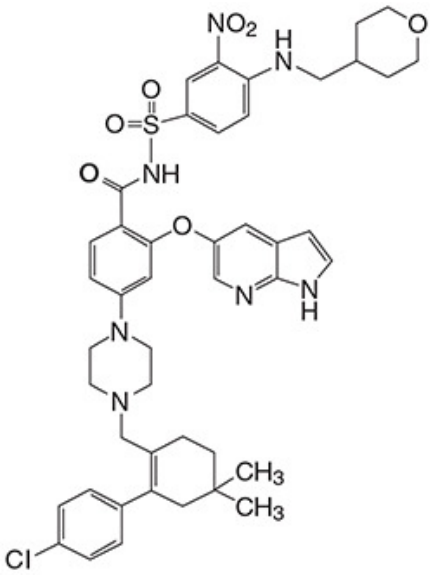
Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions *[see Dosage and Administration (2.5, 2.7) and Clinical Pharmacology (12.3)]*.

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, 2.4, 2.5)]*. 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 BCL-2 inhibitor. 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 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:



Venetoclax has very low aqueous solubility.

VENCLEXTA tablets for oral use 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 trial 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_{0-24h} was 32.8 ± 16.9 mcg•h/mL following administration of 400 mg once daily with a low-fat meal. Venetoclax steady state AUC increased proportionally over the dose range of 150 to 800 mg (0.25 to 1.33 times the maximum approved recommended dosage). The pharmacokinetics of venetoclax does not change over time.

Absorption

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

Effect of Food

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

After single oral dose of radiolabeled [^{14}C]-venetoclax 200 mg to healthy subjects, >99.9% of the dose was recovered in feces (21% as unchanged) and <0.1% in urine within 9 days.

Specific Populations

No clinically significant differences in the pharmacokinetics of venetoclax were observed based on age (19 to 93 years), sex, weight, mild to ~~moderate~~ severe renal impairment (CLcr 15~~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~~ end-stage renal ~~impairment~~ disease (CLcr < ~~30~~ 15 mL/min) or dialysis on venetoclax pharmacokinetics is unknown.

Racial or Ethnic Groups

No clinically significant differences in the pharmacokinetics of venetoclax were observed in White, Black, and Asian patients enrolled in the United States. Of 771 patients with AML, Asian patients from Asian countries [China (5.6%), Japan (5.5%), South Korea (2.1%), and Taiwan (0.9%)] had 63% higher venetoclax exposure than non-Asian populations.

Patients with Hepatic Impairment

Following a single dose of VENCLEXTA 50 mg, venetoclax systemic exposure ($AUC_{0\text{-}INF}$) was 2.7-fold higher in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function *[see Dosage and Administration (2.7) and Use in Specific Populations (8.7)]*. No clinically relevant differences in venetoclax systemic exposure were observed between subjects with mild or moderate hepatic impairment and subjects with normal hepatic function.

Drug Interactions Studies

Clinical Studies

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

Ketoconazole

Concomitant use of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) 400 mg once daily for 7 days increased venetoclax C_{max} by 130% and $AUC_{0\text{-}INF}$ by 540% *[see Drug Interactions (7.1)]*.

Ritonavir

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

Posaconazole

Concomitant use of posaconazole (a strong CYP3A and P-gp inhibitor) 300 mg with VENCLEXTA 50 mg and 100 mg for 7 days resulted in 61% and 86% higher venetoclax C_{max}, respectively, compared with VENCLEXTA 400 mg administered alone. The venetoclax $AUC_{0\text{-}24h}$ was 90% and 144% higher, respectively *[see Drug Interactions (7.1)]*.

Rifampin

Concomitant use of a single dose of rifampin (an OATP1B1/1B3 and P-gp inhibitor) 600 mg increased venetoclax C_{max} by 106% and $AUC_{0\text{-}INF}$ by 78%. Concomitant use of multiple doses of rifampin (as a strong CYP3A inducer) 600 mg once daily for 13 days decreased venetoclax C_{max} by 42% and $AUC_{0\text{-}INF}$ by 71% *[see Drug Interactions (7.1)]*.

Warfarin

Concomitant use of a single 400 mg dose of VENCLEXTA with 5 mg of warfarin resulted in 18% to 28% increase in C_{max} and $AUC_{0\text{-}INF}$ of R-warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

Digoxin

Concomitant use of a single dose of VENCLEXTA 100 mg with digoxin (a P-gp substrate) 0.5 mg increased digoxin C_{max} by 35% and $AUC_{0\text{-}INF}$ by 9% *[see Drug Interactions (7.2)]*.

In Vitro Studies

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Neither venetoclax nor M27, a major human metabolite, were carcinogenic in a 6-month transgenic (Tg.rasH2) mouse study at oral doses up to 400 mg/kg/day of venetoclax, and at a single oral dose level of 250 mg/kg/day of M27.

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

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluate mating, fertilization, and embryonic development through implantation. There were no effects of venetoclax on estrous cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day. However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at exposures as low as 0.5 times the human AUC exposure at a dose of 400 mg.

13.2 Animal Toxicology and/or Pharmacology

In dogs, venetoclax caused single-cell necrosis in various tissues, including the gallbladder, exocrine pancreas, and stomach with no evidence of disruption of tissue integrity or organ

dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

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

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

In Combination with Obinutuzumab

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

All patients received obinutuzumab at 1000 mg on Days 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2), 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle for a total of 6 cycles. Patients in the VEN+G arm began the VENCLEXTA 5-week ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]* on Day 22 of Cycle 1, and received VENCLEXTA 400 mg orally once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomized to the GClb arm received chlorambucil 0.5 mg/kg orally on Day 1 and Day 15 of Cycles 1 to 12. Each cycle was 28 days.

A total of 432 patients were randomized, 216 to each arm. Baseline demographic and disease characteristics were similar between the arms. The median age was 72 years (range: 41 to 89 years), 89% were White, 67% were male; 36% and 43% were Binet stage B and C, respectively, and 88% had Eastern Cooperative Oncology Group (ECOG) performance status <2. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLcr <70 mL/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 10%, 11q deletion in 19%, and unmutated *IgVH* in 57%.

Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median duration of follow-up for PFS was 28 months (range: 0 to 36 months).

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

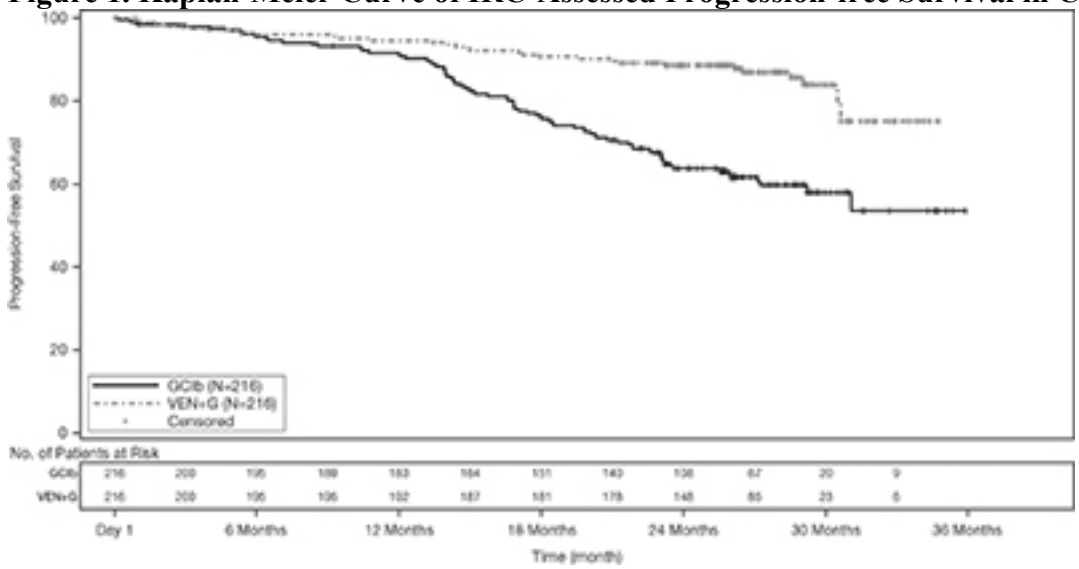
Table 19. Efficacy Results in CLL14

Endpoint	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Progression-free survival[a]		

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

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

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



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

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

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

	VENCLEXTA + Obinutuzumab	**Obinutuzumab + Chlorambucil**
MRD negativity rate (ITT population)		
N	216	216
Bone marrow, n (%)	123 (57)	37 (17)
95% CI	(50, 64)	(12, 23)
p-value[a]	<0.0001	
Peripheral blood, n (%)	163 (76)	76 (35)
95% CI	(69, 81)	(29, 42)
p-value[a]	<0.0001	
MRD negativity rate in patients with CR		
N	100	47
Bone marrow, n (%)	69 (69)	21 (45)
95% CI	(59, 78)	(30, 60)
p-value[a]	0.0048	
Peripheral blood, n (%)	87 (87)	29 (62)
95% CI	(79, 93)	(46, 75)
p-value[a]	0.0005	
CI = confidence interval; CR = complete remission. [a]p-value based on Chi-square test		

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

In Combination with Rituximab

MURANO was a randomized (1:1), multicenter, open-label trial (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 VENCLEXTA 5-week ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]*

and received VENCLEXTA 400 mg orally once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose ramp-up at a dose of 375 mg/m^2 intravenously on Day 1 of Cycle 1 and 500 mg/m^2 intravenously on Day 1 of Cycles 2-6. Patients randomized to B+R received bendamustine 70 mg/m^2 intravenously on Days 1 and 2 for 6 cycles in combination with rituximab at the above described dose and schedule. Each cycle was 28 days.

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

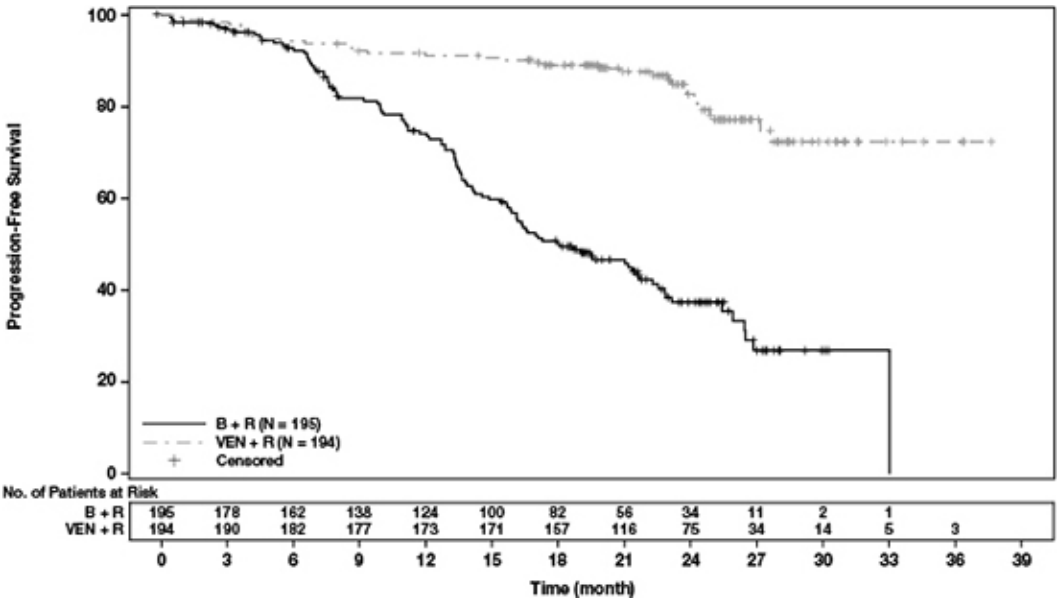
Efficacy was based on PFS as assessed by an IRC. The median follow-up for PFS was 23.4 months (range: 0 to 37.4+ months). Efficacy results for MURANO are shown in Table 21. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 21. IRC-Assessed Efficacy Results in MURANO

Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Progression-free survival[a]		
Number of events, n (%)	35 (18)	106 (54)
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; CR = complete remission; CRi = complete remission with incomplete marrow recovery; HR = hazard ratio; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission. [a]Kaplan-Meier estimate. [b]HR estimate is based on Cox-proportional hazards model stratified by 17p deletion, risk status, and geographic region; p-value based on log-rank test stratified by the same factors. [c]Per 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines.

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

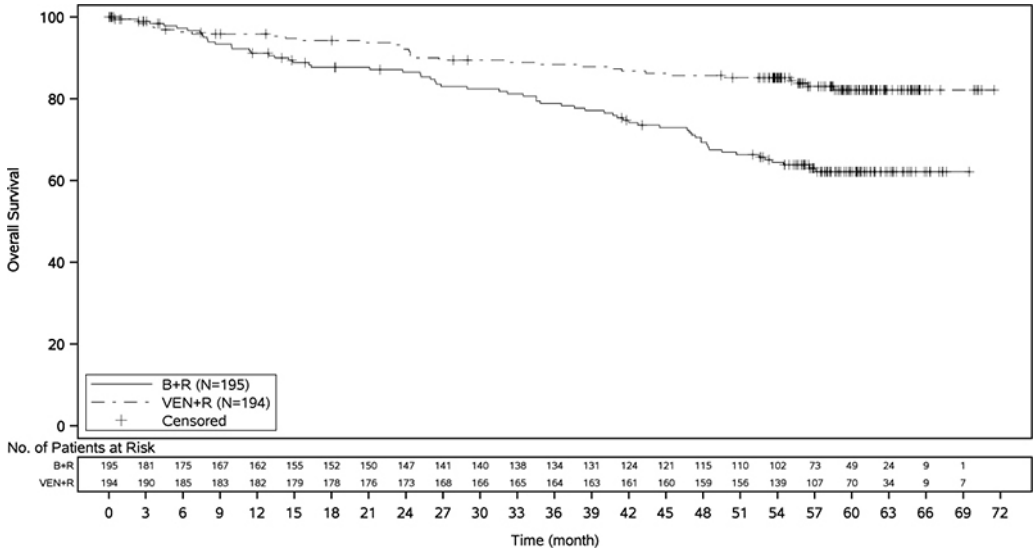


At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood in patients who achieved PR or better was 54% (104/194) in the VEN+R arm and 12% (23/195) in the B+R arm. The MRD-negative CR/CRi rate at this timepoint was 3% (6/194) in the VEN+R arm and 2% (3/195) in the B+R arm.

71-Month Follow-Up

With an overall follow-up of 71 months, the investigator-assessed median PFS was 53.6 months (95% CI: 48.4, 57.0) in the VEN+R arm and 17.0 months (95% CI: 15.5, 21.7) in the B+R arm. Median OS had not been reached in either arm. Death occurred in 16% (32/194) of patients in the VEN+R arm and 33% (64/195) of patients in the B+R arm (stratified HR 0.40; 95% CI [0.26, 0.62]). The Kaplan-Meier curve for OS is shown in Figure 3.

Figure 3. Kaplan-Meier Curve of Overall Survival in MURANO



Monotherapy

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

M13-982

M13-982 (NCT01889186) was an open-label, multicenter trial that enrolled 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the trial, 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 400 mg orally once daily following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.2, 2 .4)]*.

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

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

Table 22. Baseline Patient Characteristics in M13-982

Characteristic	N = 106
Age, years; median (range)	67 (37-83)
White; %	97
Male; %	65
ECOG performance status; % 0 1 2	 40 52 8
Tumor burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50 53

Number of prior therapies; median (range)	2.5 (1-10)
Time since diagnosis, years; median (range)[a]	6.6 (0.1-32.1)
ECOG = Eastern Cooperative Oncology Group. [a]N=105.	

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

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

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

M12-175

M12-175 (NCT01328626) was an open-label, multicenter 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 VENCLEXTA 400 mg orally once daily following completion of a ramp-up dosing schedule. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 71.7 months).

The median age was 65 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 was based on 2008 IWCLL guidelines and assessed by an IRC. The ORR was 76% (95% CI: 64%, 86%), with a CR + CRi rate of 10% and PR rate of 66%. The median DOR was 36.2 months (range: 2.4 to 52.4 months).

M14-032

M14-032 (NCT02141282) was an open-label, multicenter trial that enrolled patients with CLL who had been previously treated with and progressed on or after ibrutinib or idelalisib. Patients received VENCLEXTA 400 mg orally once daily following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]*. Patients continued this dose until disease progression or unacceptable toxicity. At the time of analysis, the median duration of treatment was 19.5 months (range: 0.1 to 39.5 months).

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

Efficacy was based on 2008 IWCLL guidelines and was assessed by an IRC. The ORR was 70% (95% CI: 61%, 78%), with a CR + CRi rate of 5% and PR rate of 65%. The median DOR was not reached with a median follow-up time of 19.9 months (range: 2.9 to 36 months).

14.2 Acute Myeloid Leukemia

VENCLEXTA was studied in adult patients with newly-diagnosed AML who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity.

In Combination with Azacitidine or Decitabine

VIALE-A was a randomized (2:1), double-blind, placebo-controlled, multicenter trial (NCT02993523) that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine (VEN+AZA) versus placebo with azacitidine (PBO+AZA).

Patients received VENCLEXTA 400 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.3)]* or placebo in combination with azacitidine 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring.

Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ⩾500/microliter and platelet count ⩾50 × 10^3/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. Azacitidine was resumed on the same day as VENCLEXTA or

placebo following interruption. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity *[see Dosage and Administration (2.5)]*. Patients continued treatment until disease progression or unacceptable toxicity.

A total of 431 patients were randomized: 286 to the VEN+AZA arm and 145 to the PBO+AZA arm. The baseline demographic and disease characteristic are shown in Table 24.

Table 24. Baseline Demographic and Disease Characteristics in Patients with AML in VIALE-A

Characteristic	VENCLEXTA + Azacitidine N = 286	Placebo + Azacitidine N = 145
Age, years; median (range)	76 (49, 91)	76 (60, 90)
Race		
White; %	76	75
Black or African American; %	1	1.4
Asian; %	23	23
Males; %	60	60
ECOG performance status; %		
0-1	55	56
2	40	41
3	5.6	3.4
Bone marrow blast; %		
<30%	30	28
≥30% to <50%	21	23
≥50%	49	49
Disease history; %		
De Novo AML	75	76
Secondary AML	25	24
Cytogenetic risk detected[a], %		
Intermediate	64	61
Poor	36	39
Mutation analyses detected; n/N[b] (%)		
IDH1 or IDH2	61/245 (25)	28/127 (22)
IDH1	23/245 (9.4)	11/127 (8.7)
IDH2	40/245 (16)	18/127 (14)
FLT3	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)

[a]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.
[b]Number of evaluable BMA specimens received at baseline.

Efficacy was based on overall survival (OS), measured from the date of randomization to death from any cause. The combination of VEN+AZA was superior in OS to PBO+AZA.

The Kaplan-Meier curve for OS is shown in Figure 4. The efficacy results of VIALE-A are shown in Table 25.

Figure 4. Kaplan-Meier Curve for Overall Survival in VIALE-A

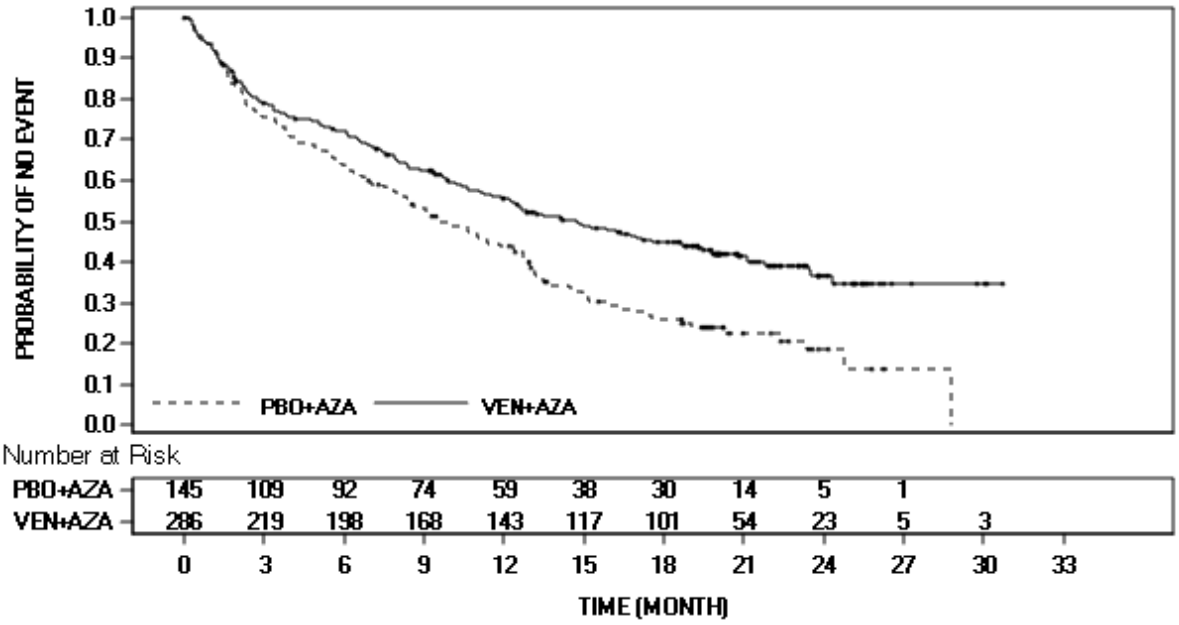


Table 25. Efficacy Results in VIALE-A

Endpoint	**VENCLEXTA + Azacitidine (N = 286)**	**Placebo + Azacitidine (N = 145)**
Overall survival		
Median[a], months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
Hazard ratio[b] (95% CI)	0.66 (0.52, 0.85)	
p-value[b]	<0.001	
Response rate		
CR, n (%)	105 (37)	26 (18)
(95% CI)	(31, 43)	(12, 25)
p-value[c]	<0.001	

Endpoint	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
Median DOCR[a,d] (months)	18.0	13.4
95% CI	(15.3, -)	(8.7, 17.6)
CR+CRh, n (%)	185 (65)	33 (23)
(95% CI)	(59, 70)	(16, 30)
p-value[c]	<0.001	
Median DOCR+CRh[a,e] (months)	17.8	13.9
95% CI	(15.3, -)	(10.4, 15.7)

CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; DOCR = duration of CR; HR = hazard ratio; - = 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).

[a]Kaplan-Meier estimate.
[b]Hazard ratio estimate (VEN+AZA vs. PBO+AZA) is based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18 to <75, ⩾75 years) as assigned at randomization; p-value based on log-rank test stratified by the same factors.

[c]p-value is from Cochran-Mantel-Haenszel test stratified by age and cytogenetics risk.

[d]Duration of CR is defined as the number of days from the date of first response of CR to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression.

[e]Duration of CR+CRh is defined as the number of days from the date of first response of CR+CRh (the first of either CR or CRh) to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression.

Among the patients treated with VEN+AZA, 155 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 49% (76/155) became independent of

RBC and platelet transfusions during any consecutive ⩾56-day post-baseline period. Of the patients treated with VEN+AZA, 131 were independent of both RBC and platelet transfusions at baseline, 69% (90/131) remained transfusion independent during any consecutive ⩾56-day post-baseline period. Among the patients treated with PBO+AZA, 81 were dependent on RBC and/or platelets transfusions at baseline; of these patients, 27% (22/81) patients became independent of RBC and platelet transfusions during any consecutive ⩾56-day post-baseline period. Of the patients treated with PBO+AZA, 64 were independent of both RBC and platelet transfusions at baseline, 42% (27/64) remained transfusion independent during any consecutive ⩾56-day post-baseline period.

The median time to first response of CR or CRh was 1.0 months (range: 0.6 to 14.3 months) with VEN+AZA treatment.

M14-358

M14-358 (NCT02203773) was a non-randomized, open-label trial that evaluated the efficacy 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 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA 400 mg orally once daily *following completion of the ramp-up dosing schedule [see Dosage and Administration (2.3)]*. in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1) or decitabine(20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1). During the ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring. Patients continued treatment until disease progression or unacceptable toxicity. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts, with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ⩾500/microliter and platelet count ⩾50 × 10^3/microliter. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity *[see Dosage and Administration (2.5)]*. Dose reductions for decitabine were not implemented in the clinical trial. Baseline demographic and disease characteristic are shown in Table 26.

Table 26. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Characteristic	VENCLEXTA + Azacitidine N = 67	VENCLEXTA + 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
Male; %	60	38
ECOG performance status; % 0-1 2 3	 64 33 3	 92 7.7 0
Disease history; % *De Novo* AML Secondary AML	 73 27	 85 15
Mutation analyses detected[a]; %		
TP53	15	31
IDH1 or IDH2	27	0
FLT3	16	23
NPM1	19	15
Cytogenetic risk detected[b,c]; %		
Intermediate	64	38
Poor	34	62
Baseline comorbidities[d]; %		
Severe cardiac disease	4.5	7.7
Severe pulmonary disease	1.5	0
Moderate hepatic impairment	9	0
Creatinine clearance <45 mL/min	13	7.7

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

The efficacy results are shown in Table 27.

Table 27 . Efficacy Results for Patients with Newly Diagnosed AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Efficacy Outcomes	VENCLEXTA + Azacitidine N = 67	VENCLEXTA+ Decitabine N = 13
CR, n (%)	29 (43)	7 (54)
(95% CI)	(31,56)	(25, 81)
CRh, n (%)	12(18)	1 (7.7)
(95% CI)	(9.6, 29)	(0.2, 36)
CI = confidence interval; CR =complete remission CRh =complete remission with partial hematological recovery.		

The median follow-up was 15.9 months (range: 0.4 to 40.3 months) for VENCLEXTA in combination with azacitidine. The median duration of CR was 23.8 months (95% CI: 15.4,-), and the median duration of CR+CRh was 26.5 months (95% CI: 17.4, -).

The median follow-up was 11.0 months (range: 0.7 to 38.8 months) for VENCLEXTA in combination with decitabine. The median duration of CR was 12.7 months (95% CI: 1.4, -) and median duration of CR+CRh was 12.7 months (95% CI: 1.4, 20.0).

Duration of CR is defined as time from the first documentation of CR to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CR+CRh is defined as time from the first documentation of either CR or CRh to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest.

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, 12% (8/67) subsequently received stem cell transplant.

The trial enrolled 35 additional patients (age range: 65 to 74 years) who did not have known comorbidities that precluded 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%). Nine (53%) 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%). Four (22%) patients subsequently received stem cell transplant.

In Combination with Low-Dose Cytarabine

VIALE-C was a randomized (2:1), double-blind, placebo-controlled, multicenter trial (NCT03069352) that evaluated the efficacy and safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) versus placebo with low-dose cytarabine (PBO+LDAC).

Patients received VENCLEXTA 600 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.3)]* or placebo in combination with cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring.

Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC $\geqslant$500/microliter and platelet count $\geqslant 50 \times 10^3$/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. LDAC was resumed on the same day as VENCLEXTA or placebo following interruption. Patients continued to receive treatment until disease progression or unacceptable toxicity. Baseline demographic and disease characteristic are shown in Table 28.

Table 28. Baseline Demographic and Disease Characteristics in Patients with AML in VIALE-C

Characteristic	VENCLEXTA + Low-Dose Cytarabine N = 143	Placebo + Low-Dose Cytarabine N = 68
Age, years; median (range)	76 (36, 93)	76 (41, 88)
Race; %		
White	71	69
Black or African American	1.4	1.5
Asian	27	29
Male; %	55	57
ECOG performance status; % 0-1 2 3	 52 44 4.2	 50 37 13
Disease history; % De Novo AML Secondary AML	 59 41	 66 34
Mutation analyses detected; n/N[a] (%)		
TP53	22/112 (20)	9/52 (17)

Characteristic	VENCLEXTA + Low-Dose Cytarabine N = 143	Placebo + Low-Dose Cytarabine N = 68
IDH1 or IDH2	21/112 (19)	12/52 (23)
FLT3	20/112 (18)	9/52 (17)
NPM1	18/112 (16)	7/52 (13)
Cytogenetic risk detected[b]; %		
Favorable	<1	4
Intermediate	63	63
Poor	33	29

[a]Number of evaluable BMA specimens received at baseline.
[b]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.

Efficacy was based on the rate of CR and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The CR rate in the VEN+LDAC arm was 27% (95% CI: 20%, 35%) with a median duration of CR of 11.1 months (95% CI: 6.1, -), and the CR rate in the PBO+LDAC arm was 7.4% (95% CI: 2.4%, 16%) with a median duration of CR of 8.3 months (95% CI: 3.1, -). The CR+CRh rate in the VEN+LDAC arm was 47% (95% CI: 39%, 55%) and in the PBO+LDAC arm was 15% (95% CI: 7.3%, 25%) with a median duration of CR+CRh of 11.1 months with VEN+LDAC treatment and 6.2 months with PBO+LDAC treatment. The median time to first response of CR or CRh was 1.0 month (range: 0.7 to 5.8 months) with VEN+LDAC treatment.

Among the patients treated with VEN+LDAC, 111 were dependent on RBC and/or platelets transfusions at baseline; of these patients, 33% (37/111) patients became independent of RBC and platelet transfusions during any consecutive ⩾56-day post-baseline period. Of the patients treated with VEN+LDAC, 32 were independent of both RBC and platelet transfusions at baseline, 50% (16/32) remained transfusion independent during any consecutive ⩾56-day post-baseline period.

Among the patients treated with PBO+LDAC, 55 were dependent on RBC and/or platelets transfusions at baseline; of these patients, 13% (7/55) patients became independent of RBC and platelet transfusions during any consecutive ⩾56-day post-baseline period. Of the patients treated with PBO+LDAC, 13 were independent of both RBC and platelet transfusions at baseline, 31% (4/13) remained transfusion independent during any consecutive ⩾56-day post-baseline period.

VEN+LDAC did not significantly improve OS versus PBO+LDAC. The hazard ratio (HR) for OS was 0.75 (95% CI: 0.52, 1.07); p-value 0.114. The median OS for VEN+LDAC arm was 7.2 months (95% CI: 5.6, 10.1) and for PBO+LDAC arm was 4.1 months (95% CI: 3.1, 8.8).

M14-387

M14-387 (NCT02287233) was a non-randomized, open-label trial that evaluated the efficacy of VEN+LDAC (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 75 years or older or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA 600 mg orally once daily on Days 1-28 following completion of the ramp-up phase *[see Dosage and Administration (2.3)]* in combination with cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC $\geqslant$500/microliter and platelet count $\geqslant 50 \times 10^3$/microliter. Patients continued treatment until disease progression or unacceptable toxicity. Baseline demographic and disease characteristic are shown in Table 29.

Table 29. 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	8.2
IDH1 or IDH2	23
FLT3	21
NPM1	9.8
Cytogenetic risk detected[b]; %	
Intermediate	59
Poor	34
No mitoses	6.6
Baseline comorbidities[c]; %	
Severe cardiac disease	9.8

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 61
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.	

The median follow-up was 7.3 months (range: 0.3 to 54.0 months). The CR rate was 21% (95% CI: 12, 34) and CRh rate was 21% (95% CI: 12, 34).

The median duration of CR was 22.9 months (95% CI: 5.1, -) and the median duration of CR+CRh was 14.3 months (95% CI: 6.1, 31.2).

Median time to first CR or CRh for patients treated with VEN+LDAC was 1.0 month (range: 0.8 to 9.4 months).

The trial enrolled 21 additional patients (age range: 67 to 74 years) who did not have known comorbidities that precluded the use of intensive induction chemotherapy and were treated with VEN+LDAC. The CR rate was 33% (95% CI:15%, 57%). The CRh rate was 24% (95% CI: 8.2%, 47%). One patient (4.8%) subsequently received stem cell transplant.

16 HOW SUPPLIED/STORAGE AND HANDLING

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets
CLL/SLL Starting Pack	Each pack contains four weekly wallet blister packs: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets)
Wallet containing 10 mg tablets	14 x 10 mg tablets
Wallet containing 50 mg tablets	7 x 50 mg tablets
Unit dose blister containing 10 mg tablets	2 x 10 mg tablets
Unit dose blister containing 50 mg tablet	1 x 50 mg tablet
Unit dose blister containing 100 mg tablet	1 x 100 mg tablet
Bottle containing 100 mg tablets	28 x 100 mg tablets
Bottle containing 100 mg tablets	120 x 100 mg tablets
Bottle containing 100 mg tablets	180 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.

Not all presentations or pack sizes may be marketed.

Store in original container at or below 30°C. Dispense to patient in original container to protect from moisture.

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

17 MANUFACTURER

AbbVie Inc., North Chicago, IL 60064, USA

18 MARKETING AUTHORISATION HOLDER

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

19 MARKETING AUTHORISATION NUMBERS

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

Revised in January ~~2023~~ 2024 ~~according to MOH guidelines.~~

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

חומר פעיל וכמותו:
כל טבליה של ונקלקסטה 10 מ"ג מכילה 10 מ"ג ונטוקלקס (venetoclax 10 mg).

כל טבליה של ונקלקסטה 50 מ"ג מכילה 50 מ"ג ונטוקלקס (venetoclax 50 mg).

כל טבליה של ונקלקסטה 100 מ"ג מכילה 100 מ"ג ונטוקלקס (venetoclax 100 mg).

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

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

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

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

1.<u>למה מיועדת התרופה?</u>

ונקלקסטה, כטיפול יחיד או בשילוב עם ריטוקסימאב, מיועדת לטיפול בחולים עם לוקמיה לימפוציטית כרונית (Chronic Lymphocytic Leukemia [CLL]) או בחולים עם לימפומה של לימפוציטים קטנים (Small Lymphocytic Lymphoma [SLL]) שקיבלו לפחות טיפול קודם אחד.

ונקלקסטה, בשילוב עם אובינוטוזומאב, מיועדת לטיפול בחולים שלא קיבלו טיפול קודם הסובלים מלוקמיה לימפוציטית כרונית (Chronic Lymphocytic Leukemia [CLL]) או בחולים עם לימפומה של לימפוציטים קטנים (Small Lymphocytic Lymphoma [SLL]).

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

קבוצה תרפויטית: אנטינאופלסטי, מעכב BCL-2.

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

2. <u>לפני השימוש בתרופה</u>

אין להשתמש בתרופה אם:

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

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

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

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

לפני הטיפול בונקלקסטה, ספר לרופא אם :

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

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

תסמונת פירוק הגידול ([Tumor Lysis Syndrome [TLS)

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 ([Tumor Lysis Syndrome [TLS).

TLS יכולה לגרום לאי ספיקת כליות, לצורך בטיפול דיאליזה, הפרעות בקצב הלב, פרכוסים ועלולה להוביל למוות.

הסיכון ל- TLS הוא בשבועות 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) .
ספר מיד לרופא, לרוקח או לאחות שלך, אם יש לך 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.
ייתכן והרופא שלך יתאים את המינון או יפסיק את הטיפול שלך בגלל תופעות לוואי.
כאשר מתחילים מחדש את הטיפול בונקלקסטה לאחר הפסקה של שבוע או יותר, הרופא שלך עשוי לבדוק שוב את הסיכון שלך ל- TLS ולשנות את המינון שלך.

ילדים ומתבגרים
לא קיים מידע לגבי בטיחות ויעילות השימוש בתכשיר זה בילדים ובמתבגרים.

אינטראקציות/תגובות בין תרופתיות

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

ספר לרופא שלך או לרוקח 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 לטיפול בזיהום 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 – וארפרין
- תרופה המשמשת לטיפול בבעיות לב המוכרת בשם דיגוקסין
- תרופה לסרטן המוכרת בשם אברולימוס
- תרופה המשמשת למניעת דחיית איברים המוכרת בשם סירולימוס

שימוש בתרופה ומזון
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 הונקלקסטה בדמך.

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

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

הנקה
אם את מניקה או מתכננת להניק, יש ליידע את הרופא שלך, הרוקח או האחות לפני נטילת תרופה זו. לא ידוע אם המרכיב הפעיל בונקלקסטה עובר לחלב אם. אין להניק במהלך הטיפול ובמשך שבוע לאחר המנה האחרונה של ונקלקסטה.

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 או סחרחורת לאחר נטילת ונקלקסטה, שיכולה להשפיע על יכולתך לנהוג או להפעיל מכונות.

3. כיצד תשתמש בתרופה?

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

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

ייתכן ותצטרך לקחת ונקלקסטה בבית חולים כדי לעקוב אחר תסמונת פירוק הגידול (TLS).

ספר לרופא שלך אם אתה מתקשה לבלוע טבליות של ונקלקסטה 100 מ"ג. הרופא שלך יכול לתת לך את אותו המינון בטבליות קטנות יותר.

עבור חולי CLL או SLL

המינון המקובל בדרך כלל הוא:

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

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

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

המינון המקובל בדרך כלל הוא:

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

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

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

המינון המקובל בדרך כלל הוא:

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

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

אין לעבור על המנה המומלצת.

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

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

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

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

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

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

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

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.

אין להפסיק לקחת ונקלקסטה
גם אם חל שיפור במצב בריאותך, אין להפסיק את הטיפול בתרופה ללא התייעצות עם הרופא.
אין ליטול תרופות בחושך! בדוק את התווית והמנה <u>בכל פעם</u> שהנך לוקח תרופה. הרכב משקפיים אם הנך זקוק להם.
אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

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

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

- התקפי עוויתות או פרכוסים

ספירה נמוכה של תאי דם לבנים (נויטרופניה) (תופעת לוואי שכיחה מאוד - עלולה להשפיע על יותר מ- 1 מתוך 10 אנשים)**:** ספירה נמוכה של תאי דם לבנים נפוצה במהלך הטיפול בונקלקסטה אך יכולה להיות חמורה. הרופא יבדוק את ספירת הדם שלך במהלך הטיפול עם ונקלקסטה וייתכן שישהה (יעצור זמנית) את הטיפול.

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

ספר לרופא אם אתה מבחין באחת מתופעות הלוואי הבאות:

<u>בחולי CLL או SLL</u>

תופעות לוואי שכיחות מאוד (עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים)
- זיהום בדרכי הנשימה העליונות - הסימנים כוללים נזלת, כאב גרון או שיעול
- שלשול
- הרגשת חולי (בחילות או הקאות)
- עצירות
- הרגשת עייפות
- שיעול
- כאבי שרירים או מפרקים
- נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים
- כאב ראש
- פריחה
- חום
- דלקת בדרכי הנשימה התחתונות
- כאבי בטן
- דלקת וכאב של רקמות הפה, הוושט והמעי (mucositis)
- סחרחורת
- קוצר נשימה
- דלקת ריאות

בנוסף, ניתן לראות בבדיקות דם:
- ספירה נמוכה של תאי דם אדומים (אנמיה)
- ספירה נמוכה של תאי דם לבנים (נויטרופניה, לימפופניה או לויקופניה בפרט)
- עלייה ברמות מלחי גוף (אלקטרוליטים) הכוללים פוספאט או אשלגן
- ירידה ברמות מלחי גוף (אלקטרוליטים) הכוללים פוספאט, סידן או נתרן
- ספירה נמוכה של טסיות
- רמות גבוהות של אנזימי כבד הנקראים אספרטט אמינוטרנספראז ([aspartate aminotransferase [AST/GOT
- רמות גבוהות של סוכר בדם
- רמות נמוכות של חלבון הנקרא אלבומין
- רמות גבוהות של חומצה אורית
- רמות גבוהות של קראטינין בדם

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

בנוסף, ניתן לראות בבדיקות דם:
- עלייה ברמות מלחי גוף (אלקטרוליטים) הכוללים סידן ומגנזיום
- ירידה ברמת מלח גוף (אלקטרוליט) הנקרא אשלגן
- רמות נמוכות של סוכר בדם

בחולי AML

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

- הרגשת חולי (בחילות או הקאות)
- שלשול
- כיבים בחלל הפה
- עצירות
- נפיחות של הזרועות, הרגליים, כפות הידיים וכפות הרגליים
- הרגשת עייפות
- דלקת ריאות
- חום עם ספירה נמוכה של תאי דם לבנים (חום נויטרופני)
- זיהום חמור בדם (אלח דם)
- פריחה
- דימום
- קוצר נשימה
- כאב בטן
- סחרחורת
- כאב ראש
- שיעול
- כאבי גב או שרירים
- לחץ דם נמוך
- כאב גרון
- חום
- זיהום בדרכי השתן
- תאבון מופחת
- ירידה במשקל

בנוסף, ניתן לראות בבדיקות דם:

- ספירה נמוכה של טסיות
- ספירה נמוכה של תאי דם לבנים (באופן כללי, ונויטרופניה או לימפופניה, באופן ספציפי)
- ספירה נמוכה של תאי דם אדומים (אנמיה)
- רמות גבוהות של בילירובין כללי
- רמות נמוכות של אשלגן בדם

תופעות לוואי שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים)

- אבני מרה או זיהום בכיס המרה
- תסמונת פירוק הגידול

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 על-ידי כניסה לקישור :

https://sideeffects.health.gov.il

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי אריזת הקרטון. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.

תנאי אחסון:

- באריזת בקבוק, ניתן להשתמש בטבליות ונקלקסטה במשך 6 שבועות לאחר פתיחה ראשונה. **אין** להעביר את הטבליות לקופסה המיועדת לטבליות או למיכל אחר.
- יש לאחסן בטמפרטורה מתחת ל- 30°c.
- יש לאחסן באריזה המקורית על מנת להגן מפני לחות.
- 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 :

- המרכיבים הנוספים בליבת הטבליה הם:

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

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

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

- הציפוי בצבע בז' של טבליית 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 טבליית ה- 100 מ"ג מכיל:

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

כיצד נראית ונקלקסטה ומה תוכן האריזה:

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

ונקלקסטה משווקת באריזות הבאות:

צורת אריזה	מספר הטבליות
CLL/SLL אריזה התחלתית	כל אריזה מכילה ארבע חפיסות בליסטרים (מגשיות) שבועיות: • שבוע 1 (14 טבליות של 10 מ"ג) • שבוע 2 (7 טבליות של 50 מ"ג) • שבוע 3 (7 טבליות של 100 מ"ג) • שבוע 4 (14 טבליות של 100 מ"ג)
חפיסת 10 מ"ג	14 טבליות של 10 מ"ג
חפיסת 50 מ"ג	7 טבליות של 50 מ"ג
יחידת מנה של 10 מ"ג	2 טבליות של 10 מ"ג
יחידת מנה של 50 מ"ג	טבליה 1 של 50 מ"ג
יחידת מנה של 100 מ"ג	טבליה 1 של 100 מ"ג
בקבוק 100 מ"ג	28 טבליות של 100 מ"ג
בקבוק 100 מ"ג	120 טבליות של 100 מ"ג
בקבוק 100 מ"ג	180 טבליות של 100 מ"ג

ייתכן ולא כל גדלי האריזה משווקים.

- בעל הרישום וכתובתו: אבווי ביופארמה בע"מ, רחוב החרש 4, הוד השרון, ישראל.
- שם היצרן וכתובתו: אבווי בע"מ ~~AbbVie Inc.~~, צפון שיקגו, IL 60064, ארה"ב.

- 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.

נערך בינואר ~~2023~~ 2024.~~בהתאם להנחיות משרד הבריאות.~~