

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrVENCLEXTA®

venetoclax tablets

Tablets, 10 mg, 50 mg and 100 mg, oral

Other Antineoplastic Agent (ATC Code: L01XX52)

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Qc H4S 1Z1

Date of Initial Authorization:
SEP 27, 2016

Date of Revision:
APR 05, 2022

Submission Control Number: 253017

RECENT MAJOR LABEL CHANGES

1 Indications	12/2020
1 Indications, 1.2 Geriatrics	04/2020
3 Serious Warnings and Precautions Box	12/2020
4 Dosage and Administration, 4.1 Dosing Considerations	12/2020
4 Dosage and Administration, 4.2 Recommended Dose and Dose Adjustment	12/2020
7 Warnings and Precautions, Carcinogenesis and Mutagenesis	01/2020
7 Warnings and Precautions, Endocrine and Metabolism	12/2020
7 Warnings and Precautions, Hematologic	12/2020
7 Warnings and Precautions, Hepatic/Biliary/Pancreatic	01/2020
7 Warnings and Precautions, Immune	12/2020
7 Warnings and Precautions, Renal	01/2020

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 5

1 INDICATIONS..... 5

 1.1 Pediatrics..... 5

 1.2 Geriatrics..... 5

2 CONTRAINDICATIONS..... 5

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 6

4 DOSAGE AND ADMINISTRATION..... 6

 4.1 Dosing Considerations 6

 4.2 Recommended Dose and Dosage Adjustment 9

 4.3 Reconstitution..... 14

 4.4 Administration 14

 4.5 Missed Dose 14

5 OVERDOSAGE..... 15

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 15

7	WARNINGS AND PRECAUTIONS.....	16
7.1	Special Populations.....	20
7.1.1	Pregnant Women.....	20
7.1.2	Breast-feeding.....	21
7.1.3	Pediatrics.....	21
7.1.4	Geriatrics.....	21
8	ADVERSE REACTIONS.....	21
8.1	Adverse Reaction Overview.....	21
8.2	Clinical Trial Adverse Reactions.....	25
8.3	Less Common Clinical Trial Adverse Reactions.....	34
8.4	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	36
8.5	Post-Market Adverse Reactions.....	41
9	DRUG INTERACTIONS.....	42
9.1	Serious Drug Interactions.....	42
9.2	Drug-Interactions Overview.....	42
9.3	Drug-Behavioural Interactions.....	42
9.4	Drug-Drug Interactions.....	42
9.5	Drug-Food Interactions.....	45
9.6	Drug-Herb Interactions.....	45
9.7	Drug-Laboratory Test Interactions.....	46
10	CLINICAL PHARMACOLOGY.....	46
10.1	Mechanism of Action.....	46
10.2	Pharmacodynamics.....	46
10.3	Pharmacokinetics.....	47
11	STORAGE, STABILITY AND DISPOSAL.....	49
12	SPECIAL HANDLING INSTRUCTIONS.....	49
PART II: SCIENTIFIC INFORMATION.....		50
13	PHARMACEUTICAL INFORMATION.....	50
14	CLINICAL TRIALS.....	51
14.1	Clinical Trials by Indication.....	51

	Chronic Lymphocytic Leukemia	51
	Acute Myeloid Leukemia	64
15	MICROBIOLOGY	71
16	NON-CLINICAL TOXICOLOGY	72
17	SUPPORTING PRODUCT MONOGRAPHS.....	73
	PATIENT MEDICATION INFORMATION	74

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- VENCLEXTA (venetoclax), in combination with obinutuzumab, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).
- VENCLEXTA, in combination with rituximab, is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- VENCLEXTA is indicated as monotherapy for the treatment of patients with CLL with 17p deletion who have received at least one prior therapy, or patients with CLL without 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options.

Clinical effectiveness of VENCLEXTA as monotherapy is based on response rate results from single-arm studies (see **14 CLINICAL TRIALS**).

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

Clinical effectiveness of VENCLEXTA in combination with low-dose cytarabine is based on response rates and transfusion independence results (see **14 CLINICAL TRIALS**).

VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program.

1.1 Pediatrics

Pediatrics (< 18 years of age): No safety and efficacy data for VENCLEXTA in children and adolescents below 18 years of age are available, therefore, Health Canada has not authorized an indication for pediatric use (see **7.1.3 Special Populations**).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No clinically meaningful differences in safety and effectiveness were observed between older and younger patients in the combination and the monotherapy studies (see **7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

- VENCLEXTA (venetoclax) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.
- In patients with CLL, concomitant use of VENCLEXTA (venetoclax) with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see **4 DOSAGE AND ADMINISTRATION** and **9 DRUG INTERACTIONS**).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

VENCLEXTA (venetoclax) should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.

VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program.

The following are significant adverse drug reactions identified in clinical trials conducted with VENCLEXTA.

- Tumour lysis syndrome (TLS) (see **7 WARNINGS AND PRECAUTIONS**).
 - Weekly dosage ramp-up over a period of 5 weeks for patients with CLL and 3 to 4 days ramp-up for patients with AML, with blood chemistry monitoring on each dose ramp-up is required (see **4 DOSAGE AND ADMINISTRATION**).
 - Patients must receive prophylaxis for TLS, including hydration and anti-hyperuricemics prior to initiating treatment (see **4 DOSAGE AND ADMINISTRATION**).
 - In patients with CLL, concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see **2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION** and **9 DRUG INTERACTIONS**).
 - In patients with AML, concomitant use of strong CYP3A inhibitors during initiation and ramp-up requires VENCLEXTA dose reduction according to **Table 7** (see **4 DOSAGE AND ADMINISTRATION** and **9 DRUG INTERACTIONS**).
- Serious infections that may lead to hospitalization or death (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Risk Assessment and Prophylaxis for Tumour Lysis Syndrome

Patients treated with VENCLEXTA (venetoclax) 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

VENCLEXTA can cause rapid reduction in tumour 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, including comorbidities, particularly reduced renal function (creatinine clearance [CrCl] < 80 mL/min) and tumour burden. Splenomegaly may contribute to the overall TLS risk. The risk may decrease as tumour burden decreases with VENCLEXTA treatment (see **7 WARNINGS AND PRECAUTIONS**).

Perform tumour 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. Blood chemistry monitoring should also be performed for all patients at 6 to 8 hours post-dose, and 24 hours post-dose for the first dose of 20 and 50 mg, and pre-dose at subsequent ramp-up doses. The next dose should not be administered until 24-hour blood chemistry results have been evaluated (see **Table 1**).

Table 1 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data. In addition, consider all patients comorbidities for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital. 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 1 – Recommended TLS Prophylaxis Based on Tumour Burden From Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumour 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 <ul style="list-style-type: none"> Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 and 50 mg Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion
Medium	Any LN 5 cm to < 10 cm OR ALC ≥ 25 x10 ⁹ /L	Oral (1.5 to 2 L) and consider additional intravenous	Allopurinol	Outpatient <ul style="list-style-type: none"> Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 and 50 mg Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion Consider hospitalization for patients with CrCl < 80 mL/min at first dose of 20 and 50 mg; see below for monitoring in hospital

Tumour Burden		Prophylaxis		Blood Chemistry Monitoring ^{c,d}
		Hydration ^a	Anti-hyperuricemics ^b	Setting and Frequency of Assessments
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 at first dose of 20 and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.

- Instruct patients to drink water daily starting 2 days before and throughout the dose ramp-up phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
- Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.
- Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
- For patients at continued risk of TLS (based on residual tumour burden, observed laboratory changes consistent with tumour lysis, or comorbidities, see **7 WARNINGS AND PRECAUTIONS**), monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Acute Myeloid Leukemia

The VENCLEXTA daily dose ramp-up is 3 days with azacitidine or 4 days with low-dose cytarabine (see **Table 3**). Based on physician's assessment, hospitalization should be considered on or before initiating VENCLEXTA until 24 hours after reaching maximum VENCLEXTA dose.

Follow the prophylaxis measures listed below:

- All patients should have white blood cell count less than 25 × 10⁹/L prior to initiation of VENCLEXTA. Cyto-reduction prior to treatment may be required.
- Prior to the first dose of VENCLEXTA and during ramp-up phase, all patients should be adequately hydrated and receive anti-hyperuricemic agents
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

4.2 Recommended Dose and Dosage Adjustment

Chronic Lymphocytic Leukemia

VENCLEXTA Dose Ramp-Up Schedule

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly ramp-up schedule to the daily dose of 400 mg over a period of 5 weeks as shown in **Table 2**. The 5-week ramp-up dosing schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of TLS.

Table 2 – Dosing Schedule for Ramp-Up Phase in Patients with CLL

Week	VENCLEXTA Daily Dose
1	20 mg (2 x 10 mg)
2	50 mg (1 x 50 mg)
3	100 mg (1 x 100 mg)
4	200 mg (2 x 100 mg)
5	400 mg (4 x 100 mg)

The Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule and also contains a Quick Start Guide for patients. The 400 mg dose is supplied in bottles of 100 mg tablets (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).

VENCLEXTA in Combination with Obinutuzumab

On Cycle 1 Day 1, start obinutuzumab administration at 100 mg, followed by 900 mg which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1, and on Day 1 of 5 subsequent cycles (total of 6 cycles, 28 days each). See GAZYVA Product Monograph for more information. Substitution of GAZYVA with any other biological medicinal product requires the consent of the prescribing physician.

On Cycle 1 Day 22, start VENCLEXTA according to the ramp-up schedule (see **Table 2**), continuing through Cycle 2 Day 28. After completing the ramp-up schedule, patients should continue VENCLEXTA 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the end of Cycle 12.

VENCLEXTA should be given for a total of 12 months as finite treatment: for six 28-day cycles in combination with obinutuzumab, followed by 6 months of VENCLEXTA as a single agent.

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the 5-week ramp-up dosing schedule with VENCLEXTA and has received VENCLEXTA at the recommended dosage of 400 mg orally once daily for 7 days (see **Table 2**). Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, at a dose of 375 mg/m² intravenous (IV) for Cycle 1 and 500 mg/m² IV for Cycles 2 through 6 (see RITUXAN PM for more detailed information).

VENCLEXTA should be administered at least 30 minutes prior to starting the rituximab infusion.

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

VENCLEXTA in Monotherapy

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

Acute Myeloid Leukemia

The dose of VENCLEXTA depends upon the combination agent. Administer VENCLEXTA according to the dosing schedule, including ramp-up, as shown in **Table 3**.

Table 3 – Dosing Schedule for Ramp-Up Phase in Patients with AML

Day	VENCLEXTA Daily Dose	
1	100 mg	
2	200 mg	
3	400 mg	
4 and beyond	400 mg when dosing in combination with azacitidine	600 mg when dosing in combination with low- dose cytarabine

Initiate VENCLEXTA administration on Cycle 1 Day 1 in combination with azacitidine (75 mg/m² administered subcutaneously on Days 1 to 7 of each 28-day cycle), or in combination with cytarabine (administered at a dose of 20 mg/m² subcutaneously once daily on Days 1 to 10 of each 28-day cycle). See the azacitidine or cytarabine injection Product Monographs for more information.

VENCLEXTA, in combination with azacitidine or low-dose cytarabine, should be continued as long as the patient is deriving clinical benefit or until unacceptable toxicity is observed. For patients without unacceptable toxicity, it is recommended that patients be treated for a minimum of 6 cycles.

Interrupt VENCLEXTA dosing as needed for management of hematologic toxicities and blood count recovery (see **Table 6**). Refer to the azacitidine or cytarabine injection Product Monographs for additional information.

Dose Modifications Based on Toxicities: Chronic Lymphocytic Leukemia

Dosing interruption and/or dose reduction for toxicities may be required. See **Table 4** for recommended dose modifications and **Table 5** for recommended dose reductions for toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of dose ramp-up schedule). Patients who discontinue VENCLEXTA have to discontinue rituximab treatment.

Table 4 – Recommended VENCLEXTA Dose Modifications for Toxicities^a in CLL

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day’s dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5) (see 4 DOSAGE AND ADMINISTRATION).
		For any events of clinical TLS ^b resume at a reduced dose following resolution (see Table 5) (see 4 DOSAGE AND ADMINISTRATION).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1 st occurrence	Interrupt VENCLEXTA. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required.
	2 nd and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) (see 4 DOSAGE AND ADMINISTRATION)	1 st occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
	2 nd 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.
<p>Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks.</p> <p>a. Adverse reactions were graded using NCI CTCAE version 4.0.</p> <p>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 8 ADVERSE REACTIONS).</p>		

Table 5 – Dose Reduction for Toxicity During VENCLEXTA Treatment for CLL

Dose at Interruption, mg	Restart Dose, mg ^a
400	300
300	200
200	100
100	50
50	20
20	10

a. Continue the reduced dose for 1 week before increasing the dose.

Dose Modifications Based on Toxicities: Acute Myeloid Leukemia

Dose Modification for Tumour Lysis Syndrome

If a patient meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution. During ramp-up, monitor for evidence of TLS, and manage abnormalities of serum creatinine and electrolytes promptly.

Dose Modification for Other Toxicities

Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of VENCLEXTA for adverse reactions are provided in **Table 6**.

Table 6 – Recommended Dose Modifications for Adverse Reactions in AML

Adverse Reaction	Occurrence	Dosage Modification
Hematologic Adverse Reactions		
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS)	Occurrence prior to achieving remission ^a	In most instances, do not interrupt VENCLEXTA in combination with azacitidine or low-dose cytarabine due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of VENCLEXTA in combination with azacitidine or low-dose cytarabine and monitor blood counts. Upon resolution to Grade 1 or 2, resume VENCLEXTA at the same dose in combination with azacitidine or low-dose cytarabine.

Adverse Reaction	Occurrence	Dosage Modification
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	<p>Delay subsequent cycle of VENCLEXTA in combination with azacitidine or low-dose cytarabine and monitor blood counts.</p> <p>Upon resolution to Grade 1 or 2, resume VENCLEXTA at the same dose in combination with azacitidine or low-dose cytarabine, and reduce VENCLEXTA duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.</p>
Non-Hematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities (see 8 ADVERSE REACTIONS)	Any occurrence	<p>Interrupt VENCLEXTA if not resolved with supportive care.</p> <p>Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.</p>
a. Recommend bone marrow evaluation.		

Dose Modifications for Patients with Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. A 50% reduction in the dose of VENCLEXTA throughout the initiation and ramp-up phase of treatment is recommended for patients with severe hepatic impairment; at steady state, a 50% reduction of the once daily dose is also recommended. Monitor these patients more frequently for signs of toxicity (see **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**).

Dose Modifications for Patients with Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CrCl \geq 30 mL/min). While severe renal impairment (CrCl \geq 15 mL/min and $<$ 30 mL/min) did not affect venetoclax pharmacokinetics in 6 patients with AML, clinical experience is limited and a recommended dose has not been determined for patients with severe renal impairment (CrCl $<$ 30 mL/min) or patients on dialysis (see **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**).

Dose Modifications for Use with Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Concomitant use of VENCLEXTA with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax exposure (i.e., C_{max} and AUC) and may increase VENCLEXTA toxicities, including the risk for TLS at initiation and during ramp-up phase. **Table 7** describes VENCLEXTA contraindication or dosage modification based on concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor at initiation, during, or after the ramp-up phase. Monitor patients more frequently for signs of toxicities (see **9 DRUG INTERACTIONS**).

Resume the VENCLEXTA dose 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 **9 DRUG INTERACTIONS**).

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

Inhibitors	Initiation and Ramp-Up Phase		Steady Daily Dose (After Ramp-Up Phase) ^a
Strong CYP3A inhibitor	CLL	Contraindicated	Reduce the VENCLEXTA dose to 100 mg or less
	AML	Day 1 – 10 mg	
		Day 2 – 20 mg	
		Day 3 – 50 mg	
		Day 4 – 100 mg or less	
Moderate CYP3A inhibitor	Reduce the VENCLEXTA dose by at least 50%.		
P-gp inhibitor			
<p>a. In patients with CLL, avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors. Consider alternative medications or reduce the VENCLEXTA dose as described in this table.</p>			

Dose Modification for Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use (see **1.1 INDICATIONS**).

Dose Modifications for Geriatrics (≥ 65 years of age)

No dose adjustment is necessary for elderly patients (see **1.2 INDICATIONS**).

4.3 Reconstitution

Not applicable.

4.4 Administration

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

4.5 Missed Dose

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

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

5 OVERDOSAGE

Daily doses of up to 1200 mg of venetoclax have been administered in clinical trials. Of the 5 patients who received a dose of 1200 mg, there was 1 death in the setting of TLS after dose-escalation to 1200 mg. No other increased toxicity was seen. There has been no experience with overdose in clinical trials. If an overdose is suspected, treatment should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 8 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet / 10 and 100 mg venetoclax	calcium phosphate dibasic, colloidal silicon dioxide, copovidone, iron oxide yellow, polyethylene glycol, polysorbate 80, polyvinyl alcohol, sodium stearyl fumarate, talc and titanium dioxide
oral	tablet / 50 mg venetoclax	calcium phosphate dibasic, colloidal silicon dioxide, copovidone, iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate 80, polyvinyl alcohol, sodium stearyl fumarate, talc and titanium dioxide

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.

For ramp-up dosing, VENCLEXTA is dispensed as a monthly Starting Pack. Each pack contains 4 weekly wallet blister packs, as follows:

- A Week 1 wallet blister pack containing a blister card of 14 tablets (i.e., two 10 mg tablets per day for 7 days)
- A Week 2 wallet blister pack containing a blister card of 7 tablets (i.e., one 50 mg tablet per day for 7 days)
- A Week 3 wallet blister pack containing a blister card of 7 tablets (i.e., one 100 mg tablet per day for 7 days)

- A Week 4 wallet blister pack containing a blister card of 14 tablets (i.e., two 100 mg tablets per day for 7 days)

The following individual packaging presentations are also available:

- A unit dose blister containing 2 tablets of 10 mg
- A unit dose blister containing 1 tablet of 50 mg
- A unit dose blister containing 1 tablet of 100 mg
- Bottles containing 120 tablets of 100 mg

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

In the MURANO study, second primary malignancies were more frequently reported with VENCLEXTA (venetoclax) + rituximab (11%) than bendamustine + rituximab (7%). The higher reporting rate in the VENCLEXTA + rituximab arm was primarily due to the higher frequency of non-melanoma skin malignancies (7% versus 3% in the bendamustine + rituximab arm).

In the pooled VENCLEXTA 400 mg monotherapy safety database, other malignancies, most frequently skin cancers, occurred in 18.8% of patients treated with VENCLEXTA. Non-melanoma skin cancers occurred in 9.4% of patients, and non-skin related malignancies occurred in 9.4% of patients. Causality with VENCLEXTA has not been determined.

Monitor patients for the appearance of non-melanoma skin cancers. No carcinogenicity studies of venetoclax have been performed.

Endocrine and Metabolism

Tumour Lysis Syndrome

Tumour Lysis Syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA (see **8 ADVERSE REACTIONS**).

VENCLEXTA can cause rapid reduction in tumour, and thus poses a risk for TLS at initiation and during the ramp-up phase, and during reinitiation after dosage interruption in patients with CLL. 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. Advise patients to not take their next dose until 24-hour blood chemistry results have been evaluated and they have been informed it is safe to do so (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**). TLS, including fatal cases, has been reported after a single 20 mg dose of VENCLEXTA.

The risk of TLS is a continuum based on multiple factors (see **Table 1**), including comorbidities (particularly reduced renal function), tumour burden and splenomegaly in CLL.

All patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics prior to initiation of treatment with VENCLEXTA. Monitor blood chemistries and manage abnormalities promptly (see **7 WARNINGS AND PRECAUTIONS**). Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases (see **4 DOSAGE AND ADMINISTRATION**). Interrupt dosing if needed, when restarting VENCLEXTA, follow dose modification guidance (see **4 DOSAGE AND ADMINISTRATION**).

Venetoclax is a CYP3A and P-gp substrate. Concomitant use of VENCLEXTA with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk of TLS at initiation and during ramp-up phase (see **4 DOSAGE AND ADMINISTRATION** and **9 DRUG INTERACTIONS**). In patients with CLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the 5-week ramp-up phase is contraindicated (see **2 CONTRAINDICATIONS**). For patients requiring concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors, or P-gp inhibitors, follow the recommendations for managing drug-drug interactions summarized in **Table 7** (see **9 DRUG INTERACTIONS** and **4 DOSAGE AND ADMINISTRATION**).

Monitor patients more frequently for signs of VENCLEXTA toxicities (see **4 DOSAGE AND ADMINISTRATION**).

Grapefruit products, Seville oranges, and starfruit must not be consumed during the ramp-up phase, as they contain inhibitors of CYP3A.

Hematologic

Hemorrhage

Serious and fatal hemorrhagic events have been reported in patients with AML treated with VENCLEXTA in combination with azacitidine or low-dose cytarabine. Grade ≥ 3 hemorrhagic adverse events were more frequently reported in patients treated with VENCLEXTA plus azacitidine (10.2%) or VENCLEXTA plus low-dose cytarabine (10.6%) compared to those treated with placebo plus azacitidine or low-dose cytarabine (6.3% and 7.4%, respectively).

Patients should be monitored for bleeding events, and treatment should be interrupted as appropriate (see **4 DOSAGE AND ADMINISTRATION**).

Neutropenia

Neutropenia is an identified risk with VENCLEXTA treatment.

Neutropenia (all Grades) was reported in 58% of patients in the VENCLEXTA + obinutuzumab arm of the CLL14 study. Forty-one percent experienced dose interruption, 13% had dose reduction and 2% discontinued VENCLEXTA due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and Grade 4 neutropenia in 28% of patients. The median duration of Grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). The following complications of neutropenia were reported in the VENCLEXTA + obinutuzumab arm versus the obinutuzumab + chlorambucil arm, respectively: febrile neutropenia 6% versus 4%, Grade ≥ 3 infections 19% versus 16%, and serious infections 19% versus 14%.

Neutropenia was reported in 65% of patients treated with VENCLEXTA in combination with rituximab in the MURANO study, with Grade 3 neutropenia reported in 35% of patients and Grade 4 in 27% of patients. In addition, febrile neutropenia was reported in 4% of patients. The median duration of Grade 3 or 4 neutropenia was 8 days (range: 1 to 712 days). Forty-six percent of patients treated with VENCLEXTA + rituximab experienced dose interruptions and 3% of patients discontinued VENCLEXTA due to neutropenia.

Neutropenia was reported in 51.7% of patients treated with 400 mg VENCLEXTA in monotherapy clinical trials, with Grade 3 or 4 neutropenia reported in 46% of patients (see **8 ADVERSE REACTIONS**).

In patients with AML, Grade 3 or 4 neutropenia is common before starting treatment. In clinical trials, baseline neutrophil counts worsened in 95% to 98% of patients with AML treated with VENCLEXTA in combination with azacitidine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy.

Grade ≥ 3 neutropenia was reported in 45% of patients treated with VENCLEXTA in combination with azacitidine in the VIALE-A study. The following were reported in the VENCLEXTA + azacitidine arm versus the placebo + azacitidine arm, respectively: febrile neutropenia 42% versus 19%, Grade ≥ 3 infections 64% versus 51%, and serious infections 57% versus 44%.

Grade ≥ 3 neutropenia was reported in 51% of patients treated with VENCLEXTA in combination with low-dose cytarabine in the VIALE-C study. The following were reported in the VENCLEXTA + low-dose cytarabine arm versus the placebo + low-dose cytarabine arm, respectively: febrile neutropenia 32% versus 29%, Grade ≥ 3 infections 42% versus 50%, and serious infections 35% versus 35%.

Monitor complete blood counts throughout the treatment period. Dose interruptions or dose reductions are recommended for severe neutropenia. Consider supportive measures, including antimicrobials for any signs of infection, and prophylactic use of growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) (see **4 DOSAGE AND ADMINISTRATION**).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment (see **10 CLINICAL PHARMACOLOGY**). These patients should be monitored more closely for signs of toxicity at initiation and during the dose ramp-up phase (see **8 ADVERSE REACTIONS**). A 50% reduction in the dose of VENCLEXTA throughout the initiation and ramp-up phase of treatment is recommended for patients with severe hepatic impairment; at steady state, a 50% reduction of the once daily dose is also recommended. Monitor these patients more closely for signs of toxicity (see **4 DOSAGE AND ADMINISTRATION** and **10 CLINICAL PHARMACOLOGY**).

Immune

Immunization

The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Live vaccines should not be administered during treatment with VENCLEXTA and thereafter until B-cell recovery. Advise patients that vaccinations may be less effective.

Infections

Serious and fatal infections, including events of sepsis, have been reported in patients treated with VENCLEXTA (see **8 ADVERSE REACTIONS**). Patients treated with VENCLEXTA should be monitored for fever and other signs of infection, and have their complete blood counts monitored throughout treatment, and treated promptly. Dosing should be interrupted as appropriate (see **4 DOSAGE AND ADMINISTRATION**).

In the MURANO study of patients with CLL, the frequency of infections of any Grade was higher in VENCLEXTA + rituximab arm compared with bendamustine + rituximab arm (75% vs. 62%). The most common infections in the VENCLEXTA + rituximab arm were upper and lower respiratory tract infections (see **Table 10**). Serious infections were reported in 21% of patients treated with VENCLEXTA + rituximab including 4 fatal cases (3 died from pneumonia and 1 from sepsis) compared with 24% of patients treated with bendamustine + rituximab including 4 fatal cases (2 sepsis and 1 case each of scedosporium infection and Listeria sepsis).

In the pooled VENCLEXTA 400 mg monotherapy safety database of patients with CLL, infections were reported in 80.4% of patients, with Grade ≥ 3 events for 23.9%. The most common infections identified as adverse drug reactions were upper respiratory tract infection (30.7%), pneumonia (12.8%), nasopharyngitis (11.1%), and urinary tract infection (9.4%). Serious infections were reported in 24.7% of patients treated with VENCLEXTA monotherapy, including 7 fatal cases (4 sepsis, 2 pneumonia, and 1 respiratory syncytial virus infection). The most common serious adverse reactions of infection were pneumonia (7.7%) and upper respiratory tract infection (1.4%). Causality with VENCLEXTA cannot be ruled out.

In patients with AML, the frequency of infections (all Grades) was higher in patients treated with VENCLEXTA + azacitidine (84.5%) compared to those treated with placebo + azacitidine (67.4%), and was similar between patients treated with VENCLEXTA + low-dose cytarabine (61.3%) and those treated with placebo + low-dose cytarabine (61.8%). The most commonly reported serious infections in patients treated with VENCLEXTA in combination with azacitidine or low-dose cytarabine were pneumonia and sepsis, reported in 16.6% and 5.7%, respectively, of patients treated with VENCLEXTA + azacitidine, and 12.7% and 5.6%, respectively, of patients treated with VENCLEXTA + low-dose cytarabine. Pneumonia and sepsis were also the most frequent Grade ≥ 3 infections, reported in 19.8% and 6.0%, respectively, of patients treated with VENCLEXTA + azacitidine and 16.9% and 5.6%, respectively, of patients treated with VENCLEXTA + low-dose cytarabine.

Monitoring and Laboratory Tests

Tumour burden assessments, including radiographic evaluation, should be performed for all patients prior to VENCLEXTA initiation. Blood chemistry monitoring (potassium, uric acid, phosphorous, calcium, and creatinine) should also be performed for all patients before initiating VENCLEXTA, at 6 to 8 hours post-dose, and 24 hours post-dose for the first dose of 20 and 50 mg, and pre-dose at subsequent ramp-up doses. The next dose should not be administered until 24-hour blood chemistry results have been evaluated. For patients at continued risk of TLS (based on residual tumour burden, observed laboratory changes consistent with tumour lysis, or comorbidities, see **7 WARNINGS AND PRECAUTIONS**) this same monitoring schedule should be performed when starting each subsequent ramp-up. Refer to **4 DOSAGE AND ADMINISTRATION** for additional information.

Patients treated with VENCLEXTA should be monitored for signs of infection, and have their complete blood counts monitored throughout treatment.

Patients should have their baseline renal function and hepatic status measured prior to VENCLEXTA initiation.

Renal

Renal Impairment

No specific clinical trials have been conducted in subjects with renal impairment. No dose adjustment is needed for patients with mild or moderate renal impairment ($\text{CrCl} \geq 30 \text{ mL/min}$ and $< 90 \text{ mL/min}$) based on the results of the population pharmacokinetic analysis (see **10 CLINICAL PHARMACOLOGY**). While severe renal impairment ($\text{CrCl} \geq 15 \text{ mL/min}$ and $< 30 \text{ mL/min}$) did not affect venetoclax pharmacokinetics in 6 patients with AML, clinical experience is limited and a recommended dose has not been determined for patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) or patients on dialysis.

Due to the increased risk of TLS, patients with reduced renal function ($\text{CrCl} < 80 \text{ mL/min}$) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA (see **4 DOSAGE AND ADMINISTRATION**).

Reproductive Health: Female and Male Potential

Females of reproductive potential should undergo pregnancy testing before initiation of VENCLEXTA. Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last VENCLEXTA dose.

- **Fertility**

Testicular germ cell depletion was observed in dogs. It is unknown if this finding is reversible. Based on these findings, male fertility may be compromised by treatment with VENCLEXTA (see **16 NON-CLINICAL TOXICOLOGY**).

7.1 Special Populations

7.1.1 Pregnant Women

VENCLEXTA should not be used during pregnancy.

Venetoclax may cause fetal harm if administered to pregnant women. There are no adequate and well-controlled data from the use of VENCLEXTA in pregnant women. In pregnant mice, venetoclax treatment during the period of organogenesis resulted in an increase in postimplantation loss, reduced fetal body weights, an increase in the average number of early resorptions and in the percentage of dead or resorbed conceptuses per litter (see **16 NON-CLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding

It is not known whether venetoclax or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded because many drugs are excreted in human milk.

Breastfeeding should be discontinued during treatment with VENCLEXTA.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of VENCLEXTA in children and adolescents less than 18 years of age have not been studied, therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): A total of 434 patients with CLL were evaluated for safety from the combination study of VENCLEXTA + rituximab (MURANO) and three open-label monotherapy studies. Of these, 54% were ≥ 65 years of age and 16% were ≥ 75 years of age.

No specific dose adjustment is required for elderly patients (aged ≥ 65 years). No clinically meaningful differences in safety or efficacy were observed between patients < 65 years of age and those ≥ 65 years of age in combination and monotherapy studies. In the MURANO combination study, patients ≥ 65 years of age experienced higher incidences of diarrhea, peripheral oedema, dizziness, blood creatinine increased, constipation, pyrexia, and fall than those < 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

The safety of VENCLEXTA (venetoclax) in combination with obinutuzumab (n = 212) versus obinutuzumab and chlorambucil (n = 214) was evaluated in an open-label randomized (1:1) Phase 3 study in patients with previously untreated CLL and coexisting medical conditions. Details of the study treatment are described in **14 CLINICAL TRIALS**.

The most common (≥ 20%) adverse reactions (ARs) of any grade reported in patients receiving VENCLEXTA in combination with obinutuzumab were neutropenia, and diarrhea.

The most common (≥ 5%) Grade 3/4 reactions in the VENCLEXTA + obinutuzumab patients were neutropenia, anaemia, and febrile neutropenia.

Serious adverse reactions were reported in 49.1% of patients treated with VENCLEXTA + obinutuzumab. The most frequently (≥ 2%) reported serious adverse reactions in the VENCLEXTA + obinutuzumab arm were pneumonia, sepsis, and febrile neutropenia. Deaths due to adverse event were reported in 16 patients treated with VENCLEXTA + obinutuzumab, with sepsis as the most frequent cause of death.

In the VENCLEXTA + obinutuzumab arm, adverse events led to discontinuation in 16% of patients, dose reductions in 21% of patients and dose interruptions in 74% of patients. The most common adverse reaction that led to dose interruption of VENCLEXTA was neutropenia.

VENCLEXTA in Combination with Rituximab

The safety of VENCLEXTA in combination with rituximab (n = 194) versus bendamustine in combination with rituximab (n = 188) was evaluated in an open-label, randomized Phase 3 study in patients with CLL who had received at least one prior therapy (MURANO Study; details of the study treatment are described in the **14 CLINICAL TRIALS** section). At the time of data analysis, the median duration of exposure was 22 months in the VENCLEXTA + rituximab arm compared with 6 months in the bendamustine + rituximab arm.

The most common adverse reactions ($\geq 20\%$) of any Grade with 5% higher frequency reported in the VENCLEXTA + rituximab arm were neutropenia, diarrhea, and upper respiratory tract infection. Grade 3 to 4 adverse events were reported more frequently in the VENCLEXTA + rituximab arm than in the bendamustine + rituximab arm (64% vs. 48%), mainly due to Grade 3 to 4 neutropenia (see **Table 10**).

Serious adverse reactions were reported in 46% of patients treated with VENCLEXTA + rituximab. The most frequently ($\geq 2\%$) reported serious adverse reactions in the VENCLEXTA + rituximab arm were pneumonia, febrile neutropenia, pyrexia, and TLS. Deaths due to adverse event were reported in 10 patients treated with VENCLEXTA + rituximab, with pneumonia as the most frequent cause of death. Two fatal cases of pneumonia were reported after disease progression.

Discontinuations due to adverse events occurred in 16% of patients treated with VENCLEXTA + rituximab. Dose reductions due to adverse events occurred in 15% of patients treated with VENCLEXTA + rituximab. Dose interruptions due to adverse events occurred in 71% of patients treated with VENCLEXTA + rituximab. The most common adverse reaction that led to dose interruption of VENCLEXTA was neutropenia.

VENCLEXTA as Monotherapy

The safety of VENCLEXTA has been assessed in a pooled safety database of 352 patients with previously treated CLL who were treated with VENCLEXTA in two Phase 2 trials (M13-982 and M14-032) and one Phase 1 trial (M12-175). The trials enrolled patients with previously treated CLL, including 212 patients with 17p deletion and 146 patients who had failed an inhibitor of the B-cell receptor pathway. Patients were treated with VENCLEXTA 400 mg monotherapy once daily following a dose ramp-up schedule.

The most common adverse reactions ($\geq 20\%$) of any Grade were neutropenia, diarrhea, nausea, anemia, thrombocytopenia, fatigue, upper respiratory tract infection and cough.

Serious adverse reactions were reported in 56.5% of patients. The most frequently reported serious adverse reactions ($\geq 2\%$) were pneumonia, febrile neutropenia, sepsis, pyrexia and autoimmune hemolytic anaemia. Deaths due to adverse reactions not related to disease progression were reported in 17 patients, most commonly (2 patients each) from septic shock and cardiopulmonary failure.

Discontinuations due to adverse reactions occurred in 11% of patients. The most frequently reported adverse reactions (≥ 2 patients) were thrombocytopenia, autoimmune hemolytic anemia, fatigue and multiple organ dysfunction syndrome.

Dosage reductions due to adverse reactions occurred in 14% of patients. The most frequently reported adverse reactions (≥ 5 patients) leading to dose reductions was neutropenia. Dose interruptions due to adverse reactions occurred in 40% of patients. The most frequently reported adverse reactions

(≥ 5 patients) leading to dose interruption were neutropenia, nausea, diarrhea, pneumonia, vomiting, febrile neutropenia, thrombocytopenia, hyperphosphatemia, pyrexia, tumor lysis syndrome and blood creatinine increased.

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

The safety of VENCLEXTA (400 mg daily dose) in combination with azacitidine (n = 283) versus placebo in combination with azacitidine (n = 144) was evaluated in a double-blind randomized Phase 3 study in patients with newly diagnosed AML (see **14 CLINICAL TRIALS**). At the time of the primary analysis, the median duration of treatment was 7.6 months (range: < 0.1 to 30.7 months) in the VENCLEXTA + azacitidine arm and 4.3 months (range: 0.1 to 24.0 months) in the placebo + azacitidine arm.

The most common adverse reactions (≥ 15%) of any Grade, reported by a higher percentage of patients (≥ 5% of patients) receiving VENCLEXTA + azacitidine compared to those with placebo + azacitidine were thrombocytopenia, neutropenia, nausea, febrile neutropenia, diarrhea, vomiting, anemia, decreased appetite, peripheral edema, leukopenia, and asthenia. The most common (≥ 5%) Grade ≥ 3 AEs reported in a higher percentage of patients (by ≥ 2%) in the VENCLEXTA + azacitidine arm compared to the placebo + azacitidine arm were thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, and atrial fibrillation.

In the VENCLEXTA + azacitidine arm, serious adverse reactions were reported in 83% of patients, with most frequent (≥ 5%) being febrile neutropenia (30%), pneumonia (23%), sepsis (16%) and hemorrhage (9%). Deaths due to adverse events were reported in 23% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥ 2%) being pneumonia (4%), sepsis (3%) and hemorrhage (2%).

Adverse reactions led to VENCLEXTA treatment discontinuations in 24% of patients, VENCLEXTA dose reductions in 2%, and VENCLEXTA dose interruptions in 72%. Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for ANC < 500/microL.

The most frequent adverse reactions (≥ 5%) leading to VENCLEXTA dose interruptions in the VENCLEXTA + azacitidine arm were febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), thrombocytopenia (10%) and sepsis (8%).

VENCLEXTA in Combination with Low-Dose Cytarabine

The safety of VENCLEXTA (600 mg daily dose) in combination with low-dose cytarabine (n = 142) versus placebo with low-dose cytarabine (n = 68) was evaluated in a double-blind randomized Phase 3 study, in patients with newly-diagnosed AML (see **14 CLINICAL TRIALS**). At the time of the primary analysis, the median duration of treatment was 3.9 months (range: < 0.1 to 17.1 months) in the VENCLEXTA + low-dose cytarabine arm and 1.7 months (range: 0.1 to 14.2 months) in the placebo + low-dose cytarabine arm.

The most common adverse reactions (≥ 15%) of any Grade, reported by a higher percentage of patients (≥ 5% of patients) receiving VENCLEXTA + low-dose cytarabine compared to those with placebo + low-dose cytarabine were neutropenia, thrombocytopenia, nausea, diarrhea, hypokalemia, anemia, and vomiting. The most common (≥ 5%) Grade ≥ 3 AEs reported in a higher percentage of patients (by ≥ 2%) in the VENCLEXTA + low-dose cytarabine arm compared to the placebo + low-dose cytarabine arm were neutropenia, thrombocytopenia, febrile neutropenia, anemia, and leukopenia.

Serious adverse reactions were reported in 65% of patients in the VENCLEXTA + low-dose cytarabine arm, with the most frequent ($\geq 5\%$) being pneumonia (18%), febrile neutropenia (16%), sepsis (11%), hemorrhage (9%), and thrombocytopenia (5%). Deaths due to adverse events were reported in 23% of patients who received VENCLEXTA in combination with low-dose cytarabine, with the most frequent ($\geq 2\%$) being pneumonia (5%), septic shock (3%), sepsis (3%), and acute cardiac failure (2%).

Adverse reactions led to treatment discontinuations in 25% of patients, VENCLEXTA dose reductions in 9%, and VENCLEXTA dose interruptions in 63%. Among patients who achieved bone marrow clearance of leukemia, 32% underwent dose interruptions for ANC $< 500/\mu\text{L}$.

The most frequent adverse reaction leading to venetoclax discontinuation in the VENCLEXTA + low-dose cytarabine arm was pneumonia (7%). The most frequent adverse reaction ($\geq 2\%$) leading to dose reductions in the VENCLEXTA + low-dose cytarabine arm was thrombocytopenia (1%). The most frequent adverse reactions ($\geq 5\%$) leading to dose interruption in the VENCLEXTA + low-dose cytarabine arm were neutropenia (20%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (6%), and anemia (5%).

Tumour Lysis Syndrome

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

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

In the CLL14 study, the incidence of laboratory TLS was 1% (3/212) in patients treated with VENCLEXTA + obinutuzumab (see **7 WARNINGS AND PRECAUTIONS**). All three events of laboratory TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in 2 cases in response to the TLS events.

VENCLEXTA in Combination with Rituximab

In the MURANO study, the incidence of adverse events of TLS was 3% (6/194; 1 clinical TLS, 5 laboratory TLS) in patients treated with VENCLEXTA + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to include the TLS prophylaxis and monitoring measures described in see **4 DOSAGE AND ADMINISTRATION**. All events of the TLS cases occurred during the VENCLEXTA ramp-up phase. The 6 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 dosing schedule and TLS prophylaxis and monitoring measures (see **4 DOSAGE AND ADMINISTRATION**). Common treatment-emergent laboratory abnormalities identified in the MURANO trial are presented in **Table 16**.

VENCLEXTA as Monotherapy

In the initial Phase 1 dose-finding trials, which had shorter (2- to 3-week) ramp-up phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures (see **4 DOSAGE AND ADMINISTRATION**). In 168 patients with CLL (163 previously treated, 5 previously untreated) starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg in Studies M13-982 and M14-032, the rate of TLS was 2.4%. All events either met laboratory TLS criteria or were reported as TLS events by the physician. No TLS with clinical consequences was observed in these patients (see **Table 14**).

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine or Low-Dose Cytarabine

In the randomized Phase 3 study of VENCLEXTA in combination with azacitidine (VIALE-A), the incidence of TLS in patients with AML who followed the 3-day ramp-up and TLS prophylaxis and monitoring measures was 1.1% (3/283, 1 clinical TLS). In the randomized Phase 3 study of VENCLEXTA in combination with low-dose cytarabine (VIALE-C), the incidence of TLS in patients with AML who followed the 4-day ramp-up and the TLS prophylaxis and monitoring measures was 5.6% (8/142, 4 clinical TLS, 2 of which were fatal). The studies required reduction of white blood cell count to $< 25 \times 10^9/L$ prior to VENCLEXTA initiation in addition to the dose ramp-up schedule, and standard prophylaxis and monitoring measures (see **4 DOSAGE AND ADMINISTRATION**). All cases of TLS occurred during dose ramp-up.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

Table 9 provides the adverse reactions reported in CLL14, listed by MedDRA body system organ class and reflects exposure to VENCLEXTA with a median duration of 10.5 months (range: 1 to 13.5 months) and to obinutuzumab and chlorambucil for 6 and 12 cycles, respectively.

Table 9 – Adverse Reactions Reported in ≥ 10% (All Grades) of Patients Treated with VENCLEXTA + Obinutuzumab

Adverse Reaction by Body System	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Blood & lymphatic system disorders				
Neutropenia ^a	60	56	62	52
Anaemia ^b	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 ^c	21	2	23	1
Infections & infestations disorder				
Upper respiratory tract infection ^d	17	1	17	1
<p>a. Includes the following preferred terms: Neutropenia and neutrophil count decreased.</p> <p>b. Includes the following preferred terms: Anaemia and haemoglobin decreased.</p> <p>c. Includes the following preferred terms: Fatigue, asthenia, lethargy.</p> <p>d. Includes the following preferred terms: upper respiratory tract infection, nasopharyngitis, pharyngitis, rhinitis, rhinitis allergic, laryngitis, pharyngitis streptococcal, and viral upper respiratory tract infection.</p>				

VENCLEXTA in Combination with Rituximab

Table 10 provides the adverse reactions reported in MURANO.

Table 10 – Summary of Adverse Reactions Reported with Incidence of $\geq 10\%$ and $\geq 5\%$ Higher for all Grades or $\geq 2\%$ Higher for Grade 3 or 4 in Patients Treated with VENCLEXTA + Rituximab Compared with Bendamustine + Rituximab

Adverse Reaction by Body System	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Blood & lymphatic system disorders				
Neutropenia ^a	65	62	50	44
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Infections & infestations				
Upper respiratory tract infection ^b	39	2	23	2
Lower respiratory tract infection ^c	18	2	10	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^d	19	1	13	0
Metabolism and nutrition disorders				
Tumour lysis syndrome ^e	3	3	1	1
<p>a. Includes the following preferred terms: Neutropenia and neutrophil count decreased.</p> <p>b. Includes the following preferred terms: laryngitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, upper respiratory tract infection, and viral upper respiratory tract infection.</p> <p>c. Includes the following preferred terms: bronchitis, bronchitis chronic, lower respiratory tract infection, and lung infection.</p> <p>d. Includes the following preferred terms: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.</p> <p>e. Includes 6 patients with reported adverse event of TLS, 5 patients with laboratory TLS and 1 patient with clinical TLS (defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures).</p>				

VENCLEXTA as Monotherapy

Adverse reactions described in **Table 11** below reflect exposure to single agent VENCLEXTA in 352 patients with previously treated CLL in 3 single-arm studies (M13-982, M14-032, M12-175) at the 400 mg once daily dose. The median duration of treatment was 17.9 months (range: 0 to 50.1 months).

Table 11 – Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade 3 or 4) of Patients with Previously Treated CLL

Adverse Reaction by Body System	VENCLEXTA (N = 352)	
	Any Grade (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders		
Neutropenia ^a	51.7	46
Anemia ^b	33.5	18.8
Thrombocytopenia ^c	31.5	20.5
Lymphopenia ^d	11.1	6.8
Febrile neutropenia	6.8	6.8
Gastrointestinal disorders		
Diarrhea	46	2.6
Nausea	42.6	1.1
Abdominal pain ^e	19.6	2.8
Constipation	17.3	0.3
Vomiting	16.2	1.1
Mucositis ^f	14.2	0.3
General disorders and administration site conditions		
Fatigue ^g	33.8	4.0
Oedema ^h	22.2	1.7
Pyrexia	18.8	0.6
Infections and infestations		
Upper respiratory tract infection ⁱ	41.5	1.4
Pneumonia ^j	14.8	7.7
Lower respiratory tract infection ^k	13.4	2.3
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^l	30.7	2.3
Arthralgia	13.6	0.9

	VENCLEXTA (N = 352)	
Adverse Reaction by Body System	Any Grade (%)	Grade 3 or 4 (%)
Nervous system disorders		
Headache	18.8	0.6
Dizziness ^m	14.8	0
Metabolism and nutrition disordersⁿ		
Hyperphosphataemia ^o	17.6	1.4
Hypokalemia ^p	15.6	4.8
Hypocalcaemia ^q	12.2	2.3
Hyperkalaemia ^r	11.1	1.1
Hypomagnesemia	10.8	0.3
Respiratory, thoracic, and mediastinal disorders		
Cough ^s	24.4	0
Dyspnea ^t	13.6	1.4
Skin and subcutaneous tissue disorders		
Rash ^u	18.5	0.3
<p>a. Neutropenia/neutrophil count decreased.</p> <p>b. Anaemia/haemoglobin decreased.</p> <p>c. Thrombocytopenia/platelet count decreased</p> <p>d. Lymphopenia/lymphocyte count decreased.</p> <p>e. Includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.</p> <p>f. Includes mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, and stomatitis.</p> <p>g. Includes asthenia, fatigue, and lethargy.</p> <p>h. Includes face oedema, fluid overload, oedema peripheral, peripheral swelling, and generalized oedema.</p> <p>i. Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, upper respiratory tract infection, and viral upper respiratory tract infection.</p> <p>j. Includes atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia legionella, pneumonia fungal, pneumonia respiratory syncytial viral, pneumonia viral.</p> <p>k. Includes bronchitis, bronchitis chronic, lower respiratory tract infection, lung infection.</p> <p>l. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.</p> <p>m. Includes dizziness and vertigo.</p> <p>n. Rates are based on all patients treated with venetoclax 400 mg once daily and therefore differ from those presented in Table 14 which only includes patients who followed the current dose ramp-up schedule and TLS prophylaxis measures.</p> <p>o. Hyperphosphataemia/blood phosphorus increased.</p> <p>p. Hypokalemia/blood potassium decreased.</p>		

	VENCLEXTA (N = 352)	
Adverse Reaction by Body System	Any Grade (%)	Grade 3 or 4 (%)
q. Hypocalcaemia/blood calcium decreased.		
r. Hyperkalaemia/blood potassium increased.		
s. Includes cough, productive cough, and upper-airway cough syndrome.		
t. Includes dyspnea, dyspnoea exertional, and dyspnoea at rest.		
u. Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash vesicular, and rash pruritic.		

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

Adverse reactions and laboratory abnormalities reported in VIALE-A (M15-656), presented below in **Table 12** and **Table 18**, respectively, reflect exposure to VENCLEXTA + azacitidine for a median duration of 7.6 months (range: < 0.1 to 30.7 months).

Table 12 – Common (> 10%) Adverse Reactions Reported with ≥ 5% Higher (All-Grades) or ≥ 2% Higher (Grade ≥ 3) Incidence in Patients Treated with VENCLEXTA + Azacitidine Compared with Placebo + Azacitidine

Adverse Reaction by Body System	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Thrombocytopenia ^a	51	48	41	38
Neutropenia ^b	45	45	30	28
Febrile neutropenia	42	42	19	19
Anemia ^c	28	26	21	20
Gastrointestinal disorders				
Nausea	44	2	35	< 1
Diarrhea	41	5	33	3
Vomiting	30	2	23	< 1
Stomatitis ^d	18	1	13	0
Abdominal pain ^e	18	< 1	13	0

General				
Fatigue ^f	31	6	23	2
Edema ^g	27	< 1	19	0
Infections and infestations				
Sepsis ^h	18	18	14	14
Urinary tract infection ⁱ	16	6	9	6
Metabolism and nutrition disorders				
Decreased appetite	25	4	17	< 1
Musculoskeletal and connective tissue disorders				
Arthralgia	12	< 1	5	0
Nervous system disorder				
Dizziness/syncope ^j	19	4	8	1
Respiratory, thoracic and mediastinal disorders				
Dyspnea	13	3	8	2
Vascular disorder				
Hemorrhage ^k	38	10	37	6
Hypotension ^l	12	5	8	3
<p>a. Includes thrombocytopenia and platelet count decreased.</p> <p>b. Includes neutropenia and neutrophil count decreased.</p> <p>c. Includes anemia and hemoglobin decreased.</p> <p>d. Includes stomatitis, mouth ulceration, mucosal inflammation, cheilitis, aphthous ulcer, glossitis and tongue ulceration.</p> <p>e. Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.</p> <p>f. Includes fatigue and asthenia.</p> <p>g. Includes edema peripheral, edema, generalized edema, eyelid edema, face edema, penile edema, periorbital edema, and swelling.</p> <p>h. Includes sepsis, escherichia sepsis, septic shock, bacteraemia, staphylococcal sepsis, klebsiella sepsis, pseudomonal sepsis, urosepsis, bacterial sepsis, candida sepsis, clostridial sepsis, enterococcal sepsis, fungal sepsis, neutropenic sepsis, streptococcal sepsis.</p> <p>i. Includes urinary tract infection, escherichia urinary tract infection, cystitis, urinary tract infection enterococcal, urinary tract infection bacterial, pyelonephritis acute, and urinary tract infection pseudomonal.</p> <p>j. Includes vertigo, dizziness, syncope, presyncope.</p> <p>k. Includes epistaxis, petechiae, hematoma, contusion, hematuria, conjunctival hemorrhage, hemoptysis, ecchymosis, hemorrhoidal hemorrhage, melena, gingival bleeding, injection site bruising, mouth hemorrhage, hemorrhage intracranial, purpura, vaginal hemorrhage, blood blister, cerebral hemorrhage, gastrointestinal hemorrhage, muscle hemorrhage, skin hemorrhage, subcutaneous hematoma, upper gastrointestinal hemorrhage, anal hemorrhage, cerebral hematoma, eye hemorrhage, disseminated intravascular coagulation, gastritis hemorrhagic, hematemesis, hematochezia, hemorrhage, hemorrhage</p>				

urinary tract, hemorrhagic diathesis, hemorrhagic stroke, hemorrhagic vasculitis, immune thrombocytopenic purpura, incision site hematoma, injection site hematoma, intestinal hemorrhage, lower gastrointestinal hemorrhage, mucosal hemorrhage, penile hemorrhage, perineal hematoma, periorbital hematoma, post procedural hematoma, post procedural hemorrhage, rectal hemorrhage, retinal hemorrhage, shock hemorrhagic, soft tissue hemorrhage, subdural hematoma, subdural hemorrhage, tongue hematoma, tongue hemorrhage, urethral hemorrhage, vessel puncture site hemorrhage, vitreous hemorrhage, and wound hemorrhage.

I. Includes hypotension and orthostatic hypotension.

VENCLEXTA in Combination with Low-Dose Cytarabine

Adverse reactions and laboratory abnormalities reported in VIALE-C (M16-043), presented below in **Table 13** and **Table 19**, respectively, reflect exposure to VENCLEXTA + low-dose cytarabine for a median duration of 3.9 months (range: < 0.1 to 17.1 months).

Table 13 – Common (≥ 10%) Adverse Reactions Reported with ≥ 5% Higher (All-Grade) or ≥ 2% Higher (Grade ≥ 3) Incidence in Patients Treated with VENCLEXTA + Low-Dose Cytarabine Compared with Placebo + Low-Dose Cytarabine

Adverse Reaction by Body System	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Neutropenia ^a	51	51	21	19
Thrombocytopenia ^b	50	49	44	43
Febrile neutropenia	32	32	29	29
Anemia	27	25	22	22
Gastrointestinal disorders				
Nausea	42	1	31	0
Diarrhea	28	3	16	0
Vomiting	25	< 1	13	0
Abdominal pain ^c	15	< 1	9	3
Stomatitis ^d	15	1	6	0
Infections and infestations				
Pneumonia ^e	29	24	22	22
Investigations				
Blood bilirubin increased	11	2	1	0

Adverse Reaction by Body System	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Metabolism and nutrition disorders				
Hypokalemia	28	11	22	15
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 disorder				
Headache	11	0	4	0
Dizziness/syncope ^h	12	1	6	0
Vascular disorder				
Hemorrhage ⁱ	40	11	28	7
Hypotension ^j	11	5	4	1
<p>a. Includes neutropenia and neutrophil count decreased</p> <p>b. Includes thrombocytopenia and platelet count decreased.</p> <p>c. Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.</p> <p>d. Includes stomatitis, mouth ulceration, aphthous ulcer, glossitis, mucosal inflammation and tongue ulceration.</p> <p>e. Includes pneumonia, lung infection, pneumonia fungal, pulmonary mycosis, bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, pneumonia pseudomonal.</p> <p>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.</p> <p>g. Includes fatigue and asthenia.</p> <p>h. Includes vertigo, dizziness, syncope, presyncope.</p> <p>i. Includes epistaxis, conjunctival hemorrhage, petechiae, disseminated intravascular coagulation, ecchymosis, hemoptysis, contusion, gastrointestinal hemorrhage, gingival bleeding, hematoma, melena, mouth hemorrhage, angina bullosa hemorrhagica, hematochezia, purpura, upper gastrointestinal hemorrhage, eyelid hematoma, hematuria, retinal hemorrhage, catheter site hemorrhage, cerebral hemorrhage, eye contusion, gastric hemorrhage, gastritis hemorrhagic, hemorrhage intracranial, hemorrhage subcutaneous, increased tendency to bruise, injection site bruising, lip hemorrhage, mucosal hemorrhage, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary alveolar hemorrhage, pulmonary hemorrhage, thrombocytopenic purpura, tooth pulp hemorrhage, uterine hemorrhage, vascular access site hemorrhage, vessel puncture site bruise, vessel puncture site hematoma.</p> <p>j. Includes hypotension and orthostatic hypotension.</p>				

8.3 Less Common Clinical Trial Adverse Reactions

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

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

Blood and Lymphatic System Disorders: febrile neutropenia (6%), lymphopenia (1%)

Infection and Infestation: pneumonia^a (9%), urinary tract infection^b (6%), sepsis^c (4%)

Investigations: blood creatinine increased (3%)

Metabolism and Nutrition Disorder: tumor lysis syndrome (1%)

- a. Includes the following terms: pneumonia, atypical pneumonia, pneumocystis jirovecii, pneumonia, pneumonia haemophilus, pneumonia fungal.
- b. Includes the following terms: urinary tract infection, cystitis.
- c. Includes the following terms: sepsis, septic shock, urosepsis

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

Long-term safety data (range 0 to 61.1 months), with approximately 3 years of follow-up after the end of treatment in the VENCLEXTA + obinutuzumab arm, indicate that there is generally no cumulative or unique late-onset toxicity associated with VENCLEXTA + obinutuzumab treatment.

VENCLEXTA in Combination with Rituximab

Other common adverse drug reactions (all Grades) reported in patients in the VENCLEXTA + rituximab arm of MURANO include:

Blood and Lymphatic System Disorders: anemia (16%), thrombocytopenia (15%), febrile neutropenia (4%)

Gastrointestinal Disorders: nausea (21%), constipation (14%), vomiting (8%)

General Disorders and Administration Site Conditions: fatigue (18%), pyrexia (15%)

Infections and Infestations: pneumonia (9%), urinary tract infections (6%), sepsis (1%)

Investigations: blood creatinine increase (3%)

Metabolism and Nutrition Disorders: hyperkalemia (6%), hyperphosphatemia (5%), hyperuricemia (4%), hypocalcemia (2%).

Respiratory, Thoracic and Mediastinal Disorders: cough (18%)

During treatment with single agent VENCLEXTA after completion of VENCLEXTA + rituximab combination treatment, the most common all Grade adverse reactions ($\geq 10\%$ patients) reported were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infection (11%); the most common Grade 3 or 4 adverse reaction ($\geq 2\%$ patients) was neutropenia (11%).

Long-term safety data (range 0.3 to 60.1 months), which includes approximately 2 years of follow-up after the end of treatment in the VENCLEXTA + rituximab arm, indicate that there is generally no cumulative or unique late-onset toxicity associated with VENCLEXTA + rituximab treatment.

VENCLEXTA as Monotherapy

Other common adverse drug reactions (all Grades) reported in patients treated with VENCLEXTA monotherapy include:

Infections and Infestations: urinary tract infections (9.7%), sepsis (5%)

Investigations: blood creatinine increased (8.2%)

Metabolism and Nutrition Disorders: hyperuricemia (7.4%), tumor lysis syndrome (2.8%)

Adverse reactions relevant to TLS observed in 168 patients with CLL in Studies M13-982 and M14-032 who followed the current dose ramp-up schedule and TLS prophylaxis measures described in **4 DOSAGE AND ADMINISTRATION** are presented in **Table 14**.

Table 14 – Adverse Reactions Relevant to TLS Reported in Patients with Previously Treated CLL

Adverse Reaction	VENCLEXTA (N = 168)	
	Any Grade (%)	Grade ≥ 3 (%)
TLS ^a	2.4	2.4
Hyperkalemia ^b	17.3	1.2
Hyperphosphatemia ^c	14.3	1.8
Hypocalcemia ^d	16.1	1.8
Hyperuricemia ^e	10.1	0.6

a. Laboratory abnormalities that met ≥ 2 of the following criteria within 24 hours of each other: potassium > 6 mmol/L, uric acid > 476 micromol/L, calcium < 1.75 mmol/L, or phosphorus > 1.5 mmol/L; or physician intervention.

b. Hyperkalemia/blood potassium increased.

c. Hyperphosphatemia/blood phosphorus increased.

d. Hypocalcemia/blood calcium decreased.

e. Hyperuricemia/blood uric acid increased.

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

Other adverse reactions (all Grades) reported in the VENCLEXTA + azacitidine arm are presented below:

Hepatobiliary Disorders: cholecystitis/cholelithiasis^a (4%)

Infections and Infestations: pneumonia^b (34%)

Investigations: weight decreased (13%)

Metabolism and Nutrition Disorders: tumor lysis syndrome (1%)

- a. Includes following terms: cholecystitis acute, cholelithiasis, cholecystitis, cholecystitis chronic
- b. Includes following terms: pneumonia, lung infection, bronchopulmonary aspergillosis, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, pneumonia viral, infectious pleural effusion, pneumonia haemophilus, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pulmonary mycosis, pulmonary nocardiosis, tuberculosis.

VENCLEXTA in Combination with Low-Dose Cytarabine

Other adverse reactions (all Grades) reported in the VENCLEXTA + low-dose cytarabine arm are presented below:

Hepatobiliary Disorders: cholecystitis/cholelithiasis^a (1.4%)

Infections and Infestations: sepsis^b (13%), urinary tract infection (7%)

Investigations: weight decreased (9%)

Metabolism and Nutrition Disorders: tumor lysis syndrome (6%)

Respiratory Disorders: dyspnea (7%)

- a. Includes following terms: cholecystitis acute, cholecystitis, cholecystitis chronic.
- b. Includes following terms: sepsis, septic shock, bacteraemia, neutropenic sepsis, bacterial sepsis, staphylococcal sepsis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

Table 15 provides common laboratory abnormalities reported in CLL14.

Table 15 – New or Worsening Clinically Important Laboratory Abnormalities Occurring at ≥ 10% in Patients Treated with VENCLEXTA + Obinutuzumab

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
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.				

VENCLEXTA in Combination with Rituximab

Table 16 provides common laboratory abnormalities reported in MURANO.

Table 16 – Common (≥ 10%) New or Worsening Laboratory Abnormalities^a Occurring at ≥ 5% (Any Grade) or ≥ 2% (Grade 3 or 4) Higher Incidence with VENCLEXTA + Rituximab Compared with Bendamustine + Rituximab

Parameter	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	Any Grade (%) ^a	Grade 3 or 4 (%)	Any Grade (%) ^a	Grade 3 or 4 (%)
Hematology				
Leukopenia	89	46	81	35
Lymphopenia	87	56	79	55
Neutropenia	86	64	84	59

Parameter	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	Any Grade (%) ^a	Grade 3 or 4 (%)	Any Grade (%) ^a	Grade 3 or 4 (%)
Chemistry				
Tumour lysis syndrome ^b	5	5	3	3
Hypocalcemia	62	5	51	2
Hypophosphatemia	57	14	35	4
AST/SGOT increased	46	2	31	3
Hyperuricemia	36	36	33	33
Alkaline phosphatase increased	35	1	20	1
Hyperbilirubinemia	33	4	26	3
Hyponatremia	30	6	20	3
Hypokalemia	29	6	18	3
Hyperkalemia	24	3	19	2
Hypernatremia	24	1	13	0
Hypoglycemia	16	2	7	0
<p>a. Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.</p> <p>b. Laboratory abnormalities that met ≥ 2 of the following criteria within 24 hours of each other: potassium > 6 mmol/L, uric acid > 476 micromol/L, calcium < 1.75 mmol/L, or phosphorus > 1.5 mmol/L.</p>				

VENCLEXTA as Monotherapy

Table 17 provides common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 17 – New or Worsening Laboratory Abnormalities with VENCLEXTA Monotherapy (≥ 40% Any Grade or ≥ 10% Grade 3 or 4)

	VENCLEXTA (N = 352)	
Laboratory Abnormality	Any Grade^a (%)	Grade 3 or 4 (%)
Hematology		
Leukopenia	89.5	44.0
Neutropenia	87.5	63.4
Lymphopenia	76.4	41.9
Anemia	72.7	27.6
Thrombocytopenia	66.8	33.2
Chemistry		
Hypocalcemia	87.5	12.2
Hyperglycemia	67.2	7.7
Hyperkalemia	60.1	4.9
AST increased	53.4	3.4
Hypoalbuminemia	48.9	2.0
Hypophosphatemia	46.4	11.4
Hyponatremia	41.5	9.1
a. Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.		

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

Table 18 – Common ($\geq 10\%$) New or Worsening Laboratory Abnormalities Occurring at $\geq 5\%$ (Any Grade) or $\geq 2\%$ (Grade 3 or 4) Higher Incidence with VENCLEXTA + Azacitidine Compared with Placebo + Azacitidine

Laboratory Abnormality	VENCLEXTA + Azacitidine N=283		Placebo + Azacitidine N=144	
	All Grades ^a (%)	Grade 3 or 4 (%)	All Grades ^a (%)	Grade 3 or 4 (%)
Hematology				
Anemia	61	57	56	52
Thrombocytopenia	94	88	94	80
Leukopenia	98	96	81	68
Neutropenia	98	98	88	81
Lymphopenia	91	71	72	39
Chemistry				
Alkaline phosphatase increased	42	1	29	< 1
Hyperbilirubinemia	53	7	40	4
Blood bicarbonate decreased	31	< 1	25	0
Hypocalcemia	51	6	39	9
Hyponatremia	46	14	47	8
a. Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

VENCLEXTA in Combination with Low-Dose Cytarabine

Table 19 – Common (≥ 10%) New or Worsening Laboratory Abnormalities Occurring at ≥ 5% (Any Grade) or ≥ 2% (Grade 3 or 4) Higher Incidence with VENCLEXTA + Low-Dose Cytarabine Compared With Placebo + Low-Dose Cytarabine

Laboratory Abnormality	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades ^a (%)	Grade 3 or 4 (%)	All Grades ^a (%)	Grade 3 or 4 (%)
Hematology				
Anemia	63	57	57	54
Leukopenia	95	90	75	65
Lymphopenia	92	69	65	24
Neutropenia	95	92	82	71
Thrombocytopenia	97	95	92	90
Chemistry				
Hypocalcemia	53	8	45	13
ALT/SGPT increased	30	4	26	1
AST/SGOT increased	36	6	37	1
Alkaline phosphatase increased	34	1	26	1
Hyperbilirubinemia	61	7	38	7
Hypokalemia	56	16	42	14
Hyperglycemia	52	13	59	9
Creatinine increased	32	4	35	3
Hypoalbuminemia	61	6	43	4
Hypernatremia	11	3	6	1
a. Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

8.5 Post-Market Adverse Reactions

Metabolism and nutrition disorders: tumour lysis syndrome, including fatal cases and patients requiring dialysis/hemofiltration.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

In patients with CLL, concomitant use of VENCLEXTA (venetoclax) with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see **9.4 Drug-Drug Interactions**).

9.2 Drug-Interactions Overview

Venetoclax is predominantly metabolized by CYP3A4. Venetoclax is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro.

9.3 Drug-Behavioural Interactions

No studies on the effects of VENCLEXTA on the ability to drive and use machines have been performed. VENCLEXTA has no or negligible influence on the ability to drive and use machines.

9.4 Drug-Drug Interactions

The drugs listed in these tables are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Effect of Other Drugs on VENCLEXTA

Venetoclax is a CYP3A and P-gp substrate; co-administration of VENCLEXTA with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax exposure; co-administration of VENCLEXTA with drugs that induce CYP3A may decrease venetoclax exposure (see **Table 20**).

Table 20 – Effects of Other Drugs on the Pharmacokinetics of Venetoclax

Co-administered drug	Dose of co-administered drug	Dose of Venetoclax	Venetoclax Ratio ^a (with/without co-administered drug)		Clinical Comment ^b
			C _{max}	AUC	
Strong CYP3A Inhibitors or P-gp Inhibitors					
ketoconazole (strong CYP3A, P-gp and BCRP inhibitor)	400 mg once daily, 7 days	50 mg, single dose	2.32	6.40	For patients requiring concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors, or P-gp inhibitors, VENCLEXTA dosing should be administered according to Table 7 . Monitor patients more frequently for signs of VENCLEXTA toxicities (see 4 DOSAGE AND ADMINISTRATION). Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor (see 4 DOSAGE AND ADMINISTRATION).
ritonavir (strong CYP3A, P-gp and OATP1B1/B3 inhibitor)	50 mg once daily, 14 days	10 mg, single dose	2.42	7.91	
posaconazole (strong CYP3A and P-gp inhibitor)	300 mg once daily, 7 days	50 mg once daily with posaconazole, 400 mg once daily without posaconazole	1.61	1.90	
		100 mg once daily with posaconazole, 400 mg once daily without posaconazole	1.86	2.44	
rifampin (strong P-gp inhibitor)	600 mg, single dose	200 mg, single dose	2.06	1.78	
Strong CYP3A Inducers					
rifampin (strong CYP3A inducer)	600 mg once daily, 13 days	200 mg, single dose	0.58	0.29	Avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inducers. Consider alternative treatments with less CYP3A induction.

Azithromycin					
azithromycin	500 mg on 1st day, followed by 250 mg once daily for 4 days	100 mg single dose	0.76	0.65	No dose adjustment is needed when venetoclax is co-administered with azithromycin.
<p>a. Ratios indicate venetoclax C_{max} and AUC values for co-administration of the medication with venetoclax vs. administration of venetoclax alone. A ratio of < 1 represents a decrease in venetoclax exposure while a ratio of > 1 represents an increase in venetoclax exposure. The source of evidence for all ratios is clinical trial.</p> <p>b. Some examples of strong or moderate CYP3A inhibitors or inducers, or P-gp inhibitors:</p> <ul style="list-style-type: none"> • Strong CYP3A inhibitors: itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir. • Moderate CYP3A inhibitors: ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil. • P-gp inhibitors: amiodarone, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor. • Strong CYP3A inducers: carbamazepine, phenytoin, rifampin, St. John's wort. • Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin. <p>AUC = area under the plasma concentration-time curve; C_{max} = peak plasma concentration</p>					

Gastric Acid Reducing Agents

Based on population pharmacokinetic analysis in patients with relapsed or refractory CLL, non-Hodgkin's lymphoma (NHL) and healthy subjects, gastric acid reducing agents (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) do not affect venetoclax bioavailability.

Effects of VENCLEXTA on Other Drugs

In vitro Studies

In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at clinically relevant concentrations. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7. Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K at clinically relevant concentrations.

Venetoclax is an inhibitor of P-gp and BCRP in vitro. Venetoclax may inhibit intestinal P-gp and BCRP after a therapeutic dose and alter the absorption of co-administered drugs that are P-gp or BCRP substrates (see **Table 21**).

Table 21 – Effects of Venetoclax on the Pharmacokinetics of Other Drugs

Co-administered drug	Dose of co-administered drug	Dose of Venetoclax	Co administered Drug Ratio ^a (with/without venetoclax)		Clinical Comment
			C _{max}	AUC	
digoxin (P-gp substrate)	0.5 mg, single dose	100 mg, single dose	1.35	1.09	To avoid a potential interaction in the gastrointestinal (GI) tract, narrow therapeutic range P-gp substrates (e.g., digoxin, everolimus, and sirolimus), should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA to avoid a potential interaction in the GI tract.
warfarin (anticoagulant)	5 mg, single dose	400 mg, single dose	1.18 to 1.20	1.23 to 1.28	Because venetoclax was not dosed to steady-state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.
<p>a. Ratios indicate co-administered drug C_{max} and AUC values for co-administration with venetoclax versus administration of the medication alone. A ratio of < 1 represents a decrease in the drug's exposure while a ratio of > 1 represents an increase in the drug's exposure. The source of evidence for all ratios is clinical trial.</p> <p>AUC = area under the plasma concentration-time curve; C_{max} = peak plasma concentration</p>					

9.5 Drug-Food Interactions

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

Food has an effect on venetoclax. Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions (see **10 CLINICAL PHARMACOLOGY**). VENCLEXTA should be administered with a meal.

9.6 Drug-Herb Interactions

Avoid concomitant use of St. John's wort, as this herb is a strong inducer of CYP3A.

9.7 Drug-Laboratory Test Interactions

The interactions of VENCLEXTA with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma (BCL)-2, a protein that inhibits cells from programmed cell death (apoptosis). Overexpression of BCL-2 in various hematologic malignancies contributes to cancer cell survival by binding and sequestering high levels of BH3 motif-containing pro-apoptotic proteins, and has been associated with resistance to chemotherapeutics.

Overexpression of BCL-2 has also been demonstrated in various lymphoma and leukemia cell lines.

Venetoclax helps restore the process of apoptosis by binding directly to the BH3-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, BAX, BAK, BAD, NOXA and PUMA to initiate mitochondrial outer membrane permeabilization (MOMP), the release of cytochrome *c*, and caspase activation, ultimately resulting in programmed cancer cell death (apoptosis)¹. In nonclinical studies, venetoclax has demonstrated cytotoxic activity towards a variety of tumour cells derived from B-cell and other hematologic malignancies that overexpress BCL-2.

10.2 Pharmacodynamics

Cardiac Electrophysiology

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

Primary Pharmacodynamics

Venetoclax binds to BCL-2 with subnanomolar affinity (TR-FRET K_i : < 0.010 nM) and to the related proteins BCL-X_L, BCL-W and MCL-1 with TR-FRET K_i values of 48 nM, 245 nM and > 444 nM, respectively. Venetoclax disrupts cellular BCL-2-BIM, BCL-X_L-BCL-X_S, and MCL-1-NOXA complexes with EC₅₀ values of 3 nM, 2.2 microM, and > 1 microM, respectively. These results are consistent with values calculated for venetoclax in cell killing assays with BCL-2-dependent RS4; 11 cells (EC₅₀: 8 nM) or BCL-X_L-dependent H146 cells (EC₅₀: 4.3 microM). Venetoclax induces the hallmarks of apoptotic cell death (e.g., caspase-3/7 activation, cytochrome *c* release from mitochondria, and externalization of phosphatidylserine as measured by annexin V staining) in BCL-2-dependent RS4; 11 cells at concentrations between 10 to 100 nM. These data demonstrate that venetoclax is a selective BCL-2 inhibitor that is able to induce on-target apoptotic cell death in BCL-2-dependent cancer cells.

¹ Souers, A. et al. (2013). "ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets." *Nature Med* 19(2): 202–208.

Safety Pharmacology

Venetoclax was tested in safety pharmacology assays to assess effects on the CNS, respiratory, and cardiovascular systems. In in vitro binding assays, venetoclax showed good selectivity in a panel of off-target receptors, ion channels and transporters, confirming the BCL-2 selective profile of venetoclax. The M27 metabolite produced significant displacement of control-specific binding at the delta opioid receptor (DOP $K_i = 0.65$ microM); however, when evaluated in a functional assay, agonist or antagonist activity was not observed at the DOP receptor up to a maximum concentration of 10 microM.

In mice, venetoclax had no CNS/neurobehavioral or respiratory effects up to and including the highest oral dose of 600 mg/kg ($C_{max} = 7.8$ mcg/mL; 3.7 times the human $C_{max,ss}$ at the dose of 400 mg/day).

To assess cardiovascular safety, venetoclax was tested in an in vitro human ether-a-go-go related gene (hERG) assay and in both conscious and anesthetized dogs. In hERG, an IC_{50} could not be calculated due to limited solubility (1.5 mcg/mL). In anesthetized dogs that received an intravenous infusion of venetoclax, there was a small, but significant, increase in corrected QT interval (8 msec) from baseline, as compared to vehicle at the highest achieved plasma concentration of 46 mcg/mL (22 times the human $C_{max,ss}$ at the dose of 400 mg/day). In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg ($C_{max} = 16$ mcg/mL; 7.6 times the human $C_{max,ss}$ at the dose of 400 mg/day). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (–6 to –13%) and cardiac output (–11 to –19%) at plasma concentrations of ≥ 16 mcg/mL and ≥ 32 mcg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average $C_{max} = 6.09$ mcg/mL at the 1200 mg dose).

10.3 Pharmacokinetics

The pharmacokinetic parameters of venetoclax at steady-state are shown in **Table 22**. Venetoclax steady state AUC increased proportionally over the dose range of 150 to 800 mg.

Table 22 – Summary of Venetoclax (400 mg) Pharmacokinetic Parameters in Patients with Hematological Malignancies

	C_{max} (mcg/mL)	$t_{1/2}$ (h) ^a	AUC ₀₋₂₄ (mcg*h/mL)	CL/F (L/h)	Vd _{ss} /F ^a (L)
Steady-state mean (%CV)	2.10 (53)	26 (17)	32.8 (52)	16.5 (66)	256–321 (32)
a. Based on the population PK estimate.					

Absorption

Following multiple oral administrations, maximum plasma concentration of venetoclax was reached 5 to 8 hours after dose.

Food Effect

In healthy volunteers, administration with a low-fat (25% of calories from fat) meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat (55% of calories from fat) meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions (see **9 DRUG INTERACTIONS**).

Distribution

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

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A. M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax in vitro (see **9 DRUG INTERACTIONS**).

Elimination

The population estimate for the terminal phase elimination half-life ($t_{1/2}$) of venetoclax was approximately 26 hours. After a single oral administration of 200 mg radiolabeled [14 C]-venetoclax to healthy subjects, > 99.9% of the dose was recovered in feces and < 0.1% of the dose was excreted in urine within 9 days. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces. The pharmacokinetics of venetoclax does not change over time.

Special Populations and Conditions

- **Pediatrics**

Pharmacokinetics of VENCLEXTA has not been evaluated in patients less than 18 years of age.

- **Geriatrics**

Based on population pharmacokinetic analyses, age does not have an effect on the pharmacokinetics of venetoclax.

- **Sex**

Based on population pharmacokinetic analyses, gender does not have an effect on the venetoclax clearance.

- **Ethnic Origin**

Based on population pharmacokinetic analyses with 771 subjects with AML, including 123 Asian subjects, Asian subjects had 67% higher venetoclax exposure than non-Asian populations. Based on the analysis of the safety and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

- **Hepatic Insufficiency**

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. The NCI Organ Dysfunction Working Group criteria for hepatic impairment were used in the analysis. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin > 1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin > 1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin > 3.0 ULN. In a dedicated hepatic impairment study following administration of a single dose of 50 mg venetoclax C_{max} and AUC in subjects with mild (Child-Pugh A; 7 subjects) or moderate (Child-Pugh B; 6 subjects) hepatic impairment were similar to subjects with normal hepatic function (6 subjects). In subjects with severe (Child-Pugh C; 5 subjects) hepatic impairment, the mean venetoclax C_{max} was similar to subjects with normal hepatic function. However, venetoclax AUC was 2.3- to 2.7-fold higher than subjects with normal hepatic function. Venetoclax $t_{1/2}$ was 2-fold longer in subjects with severe hepatic impairment (median $t_{1/2}$ of 46h; range 15 to 75h) compared to subjects with normal hepatic function (median $t_{1/2}$ of 17h; range 13 to 33h) (see **7 WARNINGS AND PRECAUTIONS**).

- **Renal Insufficiency**

Based on a population pharmacokinetic analysis that included 321 subjects with mild renal impairment ($CrCl \geq 60$ and < 90 mL/min, calculated by Cockcroft-Gault equation), 219 subjects with moderate renal impairment ($CrCl \geq 30$ and < 60 mL/min), 6 subjects with severe renal impairment ($CrCl \geq 15$ and < 30 mL/min) and 224 subjects with normal renal function ($CrCl \geq 90$ mL/min), venetoclax exposures in subjects with mild, moderate or severe renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with end-stage renal disease ($CrCl < 15$ mL/min) or subjects on dialysis (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

11 STORAGE, STABILITY AND DISPOSAL

Store between 2 and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

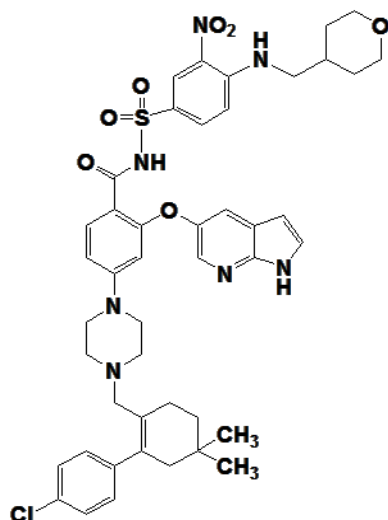
Drug Substance

Common name: venetoclax

Chemical name: 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Molecular formula and molecular mass: C₄₅H₅₀ClN₇O₇S and 868.44 g/mol

Structural formula:



Physicochemical properties: Venetoclax is a light yellow to dark yellow solid and has very low aqueous solubility.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Chronic Lymphocytic Leukemia

VENCLEXTA in Combination with Obinutuzumab

Study CLL14

CLL14 was a randomized (1:1), multicenter, open-label Phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab versus obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or creatinine clearance [CrCL] < 70 mL/min). Patients in the study were assessed for risk of tumour lysis syndrome (TLS) and received prophylaxis accordingly prior to obinutuzumab administration.

All patients received obinutuzumab at 1000 mg on Cycle 1 Day 1 (the first dose could be split as 100 and 900 mg on Days 1 and 2), and 1000 mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the VENCLEXTA + obinutuzumab arm began the 5-week VENCLEXTA ramp-up schedule (see **4 DOSAGE AND ADMINISTRATION**). After completing the ramp-up schedule on Cycle 2 Day 28, patients received VENCLEXTA 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12 as a finite treatment duration. Following completion of 12 months of VENCLEXTA, patients stopped therapy and were continued to be followed for disease progression and overall survival. Patients randomized to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1 to 12, in the absence of disease progression or unacceptable toxicity. Each cycle was 28 days.

Baseline demographic and disease characteristics were similar between the study arms (Table 23).

Table 23 – Demographics and Baseline Characteristics in CLL14

Characteristic	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Age, years; median (range)	72 (43-89)	71 (41-89)
White; %	89	90
Male; %	68	66
ECOG performance status; %		
0	41	48
1	46	41
2	13	12
CIRS score, median (range)	9 (0-23)	8 (1-28)

Characteristic	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Creatinine clearance < 70 mL/min; %	60	55
Binet Stage at screening; %		
A	21	20
B	36	37
C	43	43
CLL cytogenetics, %		
17p deletion	9	7
11q deletion	18	20
Mutation status, %		
<i>TP53</i> mutation	11	9
<i>IgVH</i> unmutated	56	57

At baseline, the median lymphocyte count was 55 x 10⁹ cells/L in both study arms. The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). The key secondary efficacy endpoints were PFS assessed by Independent Review Committee (IRC), minimal residual disease (MRD)-negativity rate (measured in peripheral blood and bone marrow), complete response rate (CRR), overall response rate (ORR), and overall survival (OS).

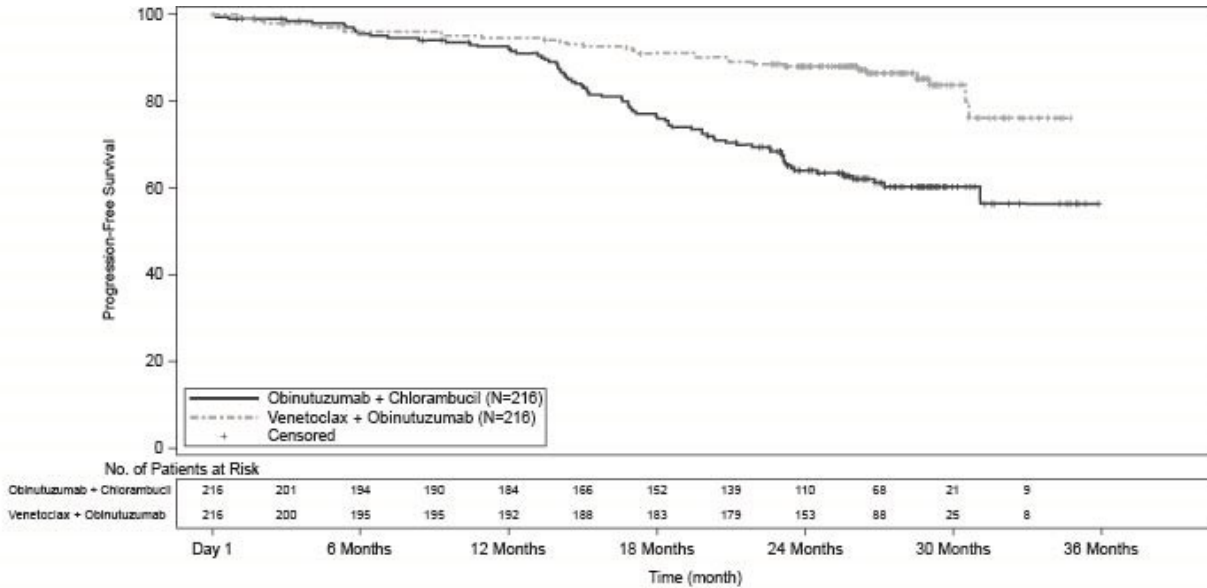
Treatment with VENCLEXTA + obinutuzumab demonstrated a statistically significant 65% reduction in the risk of disease progression or death when compared with obinutuzumab + chlorambucil treatment (stratified hazard ratio [HR] 0.35 [95% CI: 0.23 to 0.53], $p < 0.0001$, stratified log-rank test).

Efficacy results for CLL14 are shown in **Table 24**. The Kaplan-Meier curve for PFS is shown in **Figure 1**.

Table 24 – Efficacy Results for CLL14

	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Progression-free survival, investigator-assessed^a		
Number of events (%)	30 (13.9)	77 (36)
Disease progression, %	14 (6)	69 (31.9)
Death, %	16 (7.4)	8 (4)
Median, months	Not Reached	Not Reached
HR (95% CI)	0.35 (0.23, 0.53)	
p-value	< 0.0001	
Response rate		
ORR, % (95% CI)	183 (85) (79.2, 89.2)	154 (71) (64.8, 77.2)
p-value	0.0007	
CR, %	100 (46)	47 (22)
CR+CRi, %	107 (50)	50 (23)
p-value	< 0.0001	
PR, %	76 (35)	104 (48)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; INV = investigator; IRC = independent review committee; MRD = minimal residual disease; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission; HR = hazard ratio. a. From randomization until earliest event of disease progression or death due to any cause. Kaplan-Meier estimate.		

Figure 1 – Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in CLL14



Results of investigator-assessed PFS were confirmed by an IRC.

MRD was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cut-off for a negative status was < 1 CLL cell per 10⁴ leukocytes. Rates of MRD negativity regardless of response and in patients with IRC-assessed complete remission (CR/CRi) are shown in **Table 25**.

Table 25 – Minimal Residual Disease Negativity Rates Three Months After the Completion of Treatment in CLL14

	VENCLEXTA + Obinutuzumab	Obinutuzumab + Chlorambucil
MRD negativity rate in 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	

	VENCLEXTA + Obinutuzumab	Obinutuzumab + Chlorambucil
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; ITT – intent to treat; MRD = minimal residual disease.		
a. p-value based on Chi-square test.		
In paired samples, the concordance of MRD negativity between peripheral blood and bone marrow samples at end of treatment was 91% in the VENCLEXTA + obinutuzumab arm and 58% in the obinutuzumab + chlorambucil arm.		

At the time of primary PFS analysis, overall survival data were immature with death occurring in 9% of patients in the VENCLEXTA + obinutuzumab arm and 8% of patients in the chlorambucil + obinutuzumab arm.

In an exploratory analysis, statistically significant and clinically meaningful PFS benefit with VENCLEXTA + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across the following subgroups: sex; age (< 65, ≥ 65; < 75, ≥ 75); Binet stage at screening (A, B, C); B-symptoms (fever, night sweats, weight loss); estimated CrCL (< 70, ≥ 70 mL/min); del(17p)/TP53 mutation (yes, no); *IgVH* mutational status (mutated, unmutated).

52-month follow-up

With the median follow-up of 52.4 months the median PFS in the VENCLEXTA + obinutuzumab arm had not been reached [95% CI: 57.3, not reached] and median PFS in the obinutuzumab + chlorambucil arm was 36.4 months [95% CI: 34.1, 41.0].

With death having occurred in 15.7% (34/216) of patients in the VENCLEXTA + obinutuzumab arm and 19.0% (41/216) of patients in the obinutuzumab + chlorambucil arm, an overall survival benefit was not demonstrated [stratified HR 0.85; 95% CI: 0.54, 1.35].

VENCLEXTA in Combination with Rituximab

MURANO was a randomized (1:1), multicenter, open-label Phase 3 study with time-limited therapy that evaluated the efficacy and safety of VENCLEXTA (venetoclax) in combination with rituximab versus bendamustine in combination with rituximab in patients with relapsed or refractory CLL who had received at least one line of prior therapy. Patients previously treated with VENCLEXTA were excluded.

Patients in the VENCLEXTA + rituximab arm completed the 5-week ramp-up schedule of VENCLEXTA (see **4 DOSAGE AND ADMINISTRATION**) and received 400 mg VENCLEXTA daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. After the 5-week dose ramp-up, rituximab was initiated at 375 mg/m² for Cycle 1 and 500 mg/m² for Cycles 2 to 6. Each cycle was 28 days. Patients randomized to bendamustine + rituximab received bendamustine at 70 mg/m² on Days 1 and 2 for 6 cycles and rituximab at the above described dose and schedule. Following completion of the 24-month treatment in the VENCLEXTA + rituximab arm or 6 cycles of bendamustine + rituximab, patients continued to be followed for disease progression and overall survival.

A total of 389 patients were randomized; 194 to the VENCLEXTA + rituximab arm and 195 to the bendamustine + rituximab arm. Baseline demographic and disease characteristics were similar between the two arms (**Table 26**).

Table 26 – Demographics and Baseline Characteristics in MURANO

Characteristic	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Age, years; median (range)	64.5 (28–83)	66 (22–85)
White; %	96.8	96.7
Male; %	70.1	77.4
ECOG performance status; %		
0	57.2	55.7
1	42.3	43.3
2	0.5	1.0
Tumour burden; %		
Absolute lymphocyte count $\geq 25 \times 10^9/L$	66.5	68.7
One or more nodes ≥ 5 cm	45.7	47.6
Number of prior lines of therapy; %		
Median number (range)	1 (1–5)	1 (1–4)
1	57.2	60.0
2	29.4	22.1
≥ 3	13.4	17.9
Previous CLL regimens		
Median number (range)	1 (1–5)	1 (1–4)
Prior alkylating agents, %	93.3	95.4

Characteristic	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Prior purine analogs, %	80.5	81.4
Prior CD20 antibodies, %	76.3	78.6
Prior B-cell receptor pathway inhibitors, %	1.5	2.6
FCR, %	54.1	55.4
Fludarabine refractory, %	14.1	15.5
CLL cytogenetics, %		
17p deletion	26.6	27.2
11q deletion	35.3	37.9
TP53 mutation	25.0	27.7
IgVH unmutated	68.3	68.3
Time since diagnosis, years; median (range)	6.44 (0.5–28.4)	7.11 (0.3–29.5)
FCR = fludarabine, cyclophosphamide, rituximab.		

The median follow-up at the time of primary analysis was 24.8 months (range: 0.3 to 37.4 months) in the VENCLEXTA + rituximab arm and 22.1 months (range: 0 to 33.8 months) in the bendamustine + rituximab arm.

Efficacy was based on the primary endpoint of PFS as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Treatment with VENCLEXTA + rituximab demonstrated a statistically significant 81% reduction in the risk of progression or death (HR: 0.19 [95% CI: 0.13, 0.28]; $P < 0.0001$, **Table 26** and **Figure 2**).

The key secondary endpoints were CR/CRi rate, best ORR and overall survival. The CR/CRi rate was 8% in the VENCLEXTA + rituximab arm and 4% in the bendamustine + rituximab arm (**Table 26**). The CR/CRi rate difference did not reach statistical significance.

The ORR was 92% in the VENCLEXTA + rituximab arm and 72% in the bendamustine + rituximab arm (

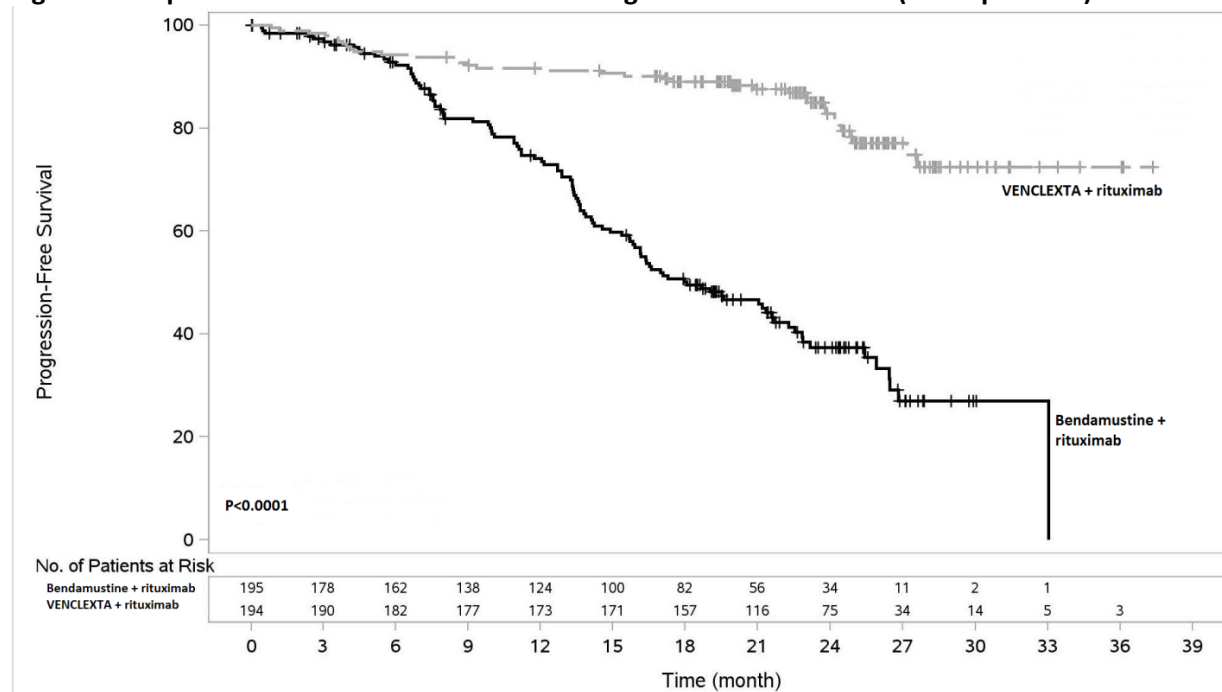
Table 27 – Efficacy Results for MURANO by IRC Assessment (ITT Population)

). At the time of the primary PFS analysis, overall survival data were immature with death occurring in 8% of patients in the VENCLEXTA + rituximab arm and 14% of patients in the bendamustine + rituximab arm. Based on the hierarchical testing plan, formal statistical testing could not be performed for ORR and overall survival.

Table 27 – Efficacy Results for MURANO by IRC Assessment (ITT Population)

	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
Progression-free survival		
Number of events (%)	35 (18.0)	106 (54.4)
Disease progression	26 (13)	91 (47)
Death events	9 (5)	15 (8)
Median, months, (95% CI)	Not reached	18.1 (15.8, 22.3)
HR (95% CI) ^a	0.19 (0.13, 0.28)	
p-value	p < 0.0001	
Response rate, %		
ORR (95% CI)	92.3 (87.6, 95.6)	72.3 (65.5, 78.5)
CR+CRi (95% CI)	8.2 (4.8, 13.1)	3.6 (1.5, 7.3)
nPR	1.5	0.5
PR	82.5	68.2
<p>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.</p> <p>a. HR = hazard ratio 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.</p>		

Figure 2 – Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival (ITT Population) in MURANO



The PFS benefit with VENCLEXTA + rituximab versus bendamustine + rituximab treatment was observed across all subgroups examined including age (< 65, ≥ 65 years and < 75, ≥ 75 years), prior lines of therapy (1, > 1), bulky disease (< 5 cm, ≥ 5 cm), 17p deletion, 11q deletion, *TP53* mutation, *IgVH* mutation, and refractory versus relapse to most recent therapy.

At the time of the primary analysis (data cut-off date 8 May 2017), 65 patients completed the 24-month VENCLEXTA + rituximab treatment regimen without progression and 78 patients were still receiving VENCLEXTA (+18 months of treatment).

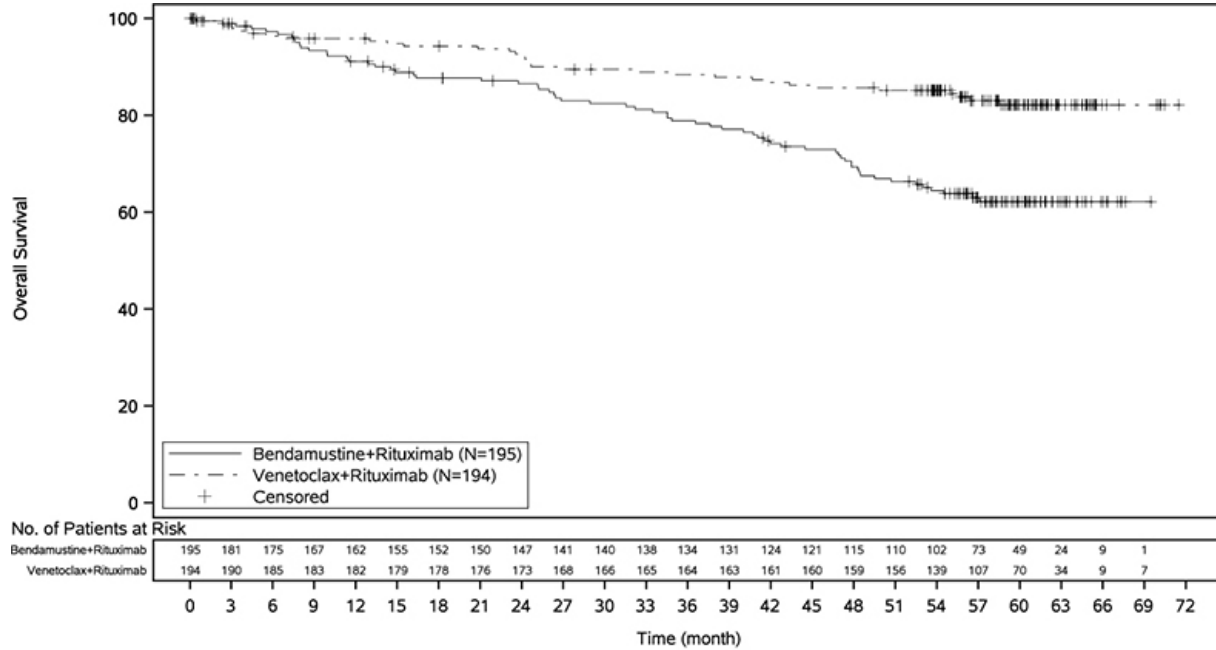
Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and flow cytometry. The cut-off for a negative status was one CLL cell per 10^4 leukocytes. At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood was 62.4% (95% CI: 55.2, 69.2) in the VENCLEXTA + rituximab arm and 13.3% (95% CI: 8.9, 18.9) in the bendamustine + rituximab arm.

59-month follow-up

With a median follow-up of 59.2 months (range 0 to 71.5 months), the investigator-assessed median PFS was 53.6 months in the VENCLEXTA + rituximab arm and 17.0 months in the bendamustine + rituximab arm (stratified hazard ratio = 0.19; 95% CI: 0.15, 0.26).

Median overall survival had not been reached in either arm. Death occurred in 16.5% (32/194) of patients in the VENCLEXTA + rituximab arm and 32.8% (64/195) of patients in the bendamustine + rituximab 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



VENCLEXTA as Monotherapy

The safety and efficacy of VENCLEXTA in patients with CLL who have received at least one prior therapy were evaluated in three single-arm studies: M13-982, M14-032 and M12-175.

Study M13-982

Study M13-982 was a Phase 2 multi-center, single-arm, open-label trial of 107 patients with previously treated CLL with 17p deletion. Patients were enrolled in the study if they had confirmed 17p deletion, and had relapsed following or were refractory after receiving at least one prior line of therapy. **Table 28** summarizes the baseline demographic and disease characteristics of the study population.

Table 28 – Demographic and Baseline Characteristics of Patients in Study M13-982

Characteristics	M13-982 N = 107 ^a
Age (years)	
Median (range)	67 (37–85)
Gender, n (%)	
Male	70 (65.4)
Female	37 (34.6)
Race, n (%)	

Characteristics	M13-982 N = 107 ^a
White	103 (97.2)
Other	4 (2.1)
Eastern Cooperative Oncology Group (ECOG) performance status	
0	39.3
1	52.3
2	8.4
Tumour burden, %	
Absolute lymphocyte count $\geq 25 \times 10^9/L$	50.5
One or more nodes > 5 cm	53.3
Number of prior therapies; median (range)	2 (1–10)
Time since diagnosis, months; median (range)	81.7 (1.2–385.6) ^b
a. One patient did not harbour the 17p deletion.	
b. N = 106.	

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

Patients received VENCLEXTA via a weekly ramp-up schedule starting at 20 mg and ramping to 50, 100, 200 and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months).

The primary efficacy endpoint was ORR as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in **Table 29**.

Table 29 – Efficacy Results in Study M13-982

Endpoint	IRC Assessment N = 107 ^a
ORR, n (%) (95% CI)	85 (79.4) (70.5, 86.6)
CR + CRi, n (%)	8 (7.5)
nPR, n (%)	3 (2.8)
PR, n (%)	74 (69.2)
<p>a. One patient did not harbour the 17p deletion. 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.</p>	

The median time to first response was 0.8 months (range: 0.1 to 8.1 months). The duration of response (DOR) ranged from 2.9 to 19.0+ months.

Based on a later data cut-off date and investigator-assessed efficacy, the DOR was evaluated in 80 patients who had a record of first response (complete remission [CR], complete remission with incomplete marrow recovery [CRi], or partial remission [PR], or nodular partial remission [nPR]). The median DOR was 35.3 months (95% CI: 26.5, NA). The Kaplan-Meier estimate for DOR at 18 and 24 months was 83.5% (95% CI: 73.3%, 90.1%) and 64.3% (95% CI: 52.6%, 73.8%), respectively.

MRD was evaluated in patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. The cut-off for a negative status was one CLL cell per 10⁴ leukocytes in the sample (i.e., an MRD value of < 10⁻⁴ was considered MRD negative). Thirty-one percent (33/107) of patients were MRD negative in the peripheral blood, including 13 patients who were also MRD negative in the bone marrow, based on investigator assessment at a later data cut-off date.

Quality of life was assessed using the cancer-specific European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. There were 73 patients who completed the Global Health Status assessment/Quality of Life subscale (GHS/QoL) at both baseline and Week 24. Patients receiving treatment with VENCLEXTA showed a 15.9% improvement in GHS/QoL mean score from baseline (58.6) to Week 24 (67.9).

Study M14-032

Study M14-032 was an open-label, multi-center, Phase 2 study that evaluated the efficacy of VENCLEXTA in patients with CLL who relapsed or were refractory to ibrutinib or idelalisib. Patients received a daily dose of 400 mg of VENCLEXTA following the ramp-up schedule. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity was observed. At the time of analysis, the median duration of treatment was 14.3 months (range: 0.1 to 31.4 months).

The primary efficacy endpoint was ORR according to IWCLL updated NCI WG guidelines (2008) and was assessed by an IRC. Response assessments were performed at Week 24 for patients in the main cohort, while patients enrolled in the expansion cohort had disease assessment at Week 36.

A total of 127 patients were enrolled in the study, which included 64 patients in the main cohort (43 with prior ibrutinib, 21 with prior idelalisib) and 63 patients in an expansion cohort (48 with prior ibrutinib, 15 with prior idelalisib). The median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3 to 18.5 years; N = 96). The median number of prior anti-CLL treatments was 4 (range: 1 to 15 treatments). Of the 127 patients, 18.9% had received both ibrutinib and idelalisib. At baseline, 41% of patients had one or more nodes ≥ 5 cm, 31% had absolute lymphocyte count $\geq 25 \times 10^9/L$, 57% had documented unmutated *IgVH*, and 39% had documented 17p deletion.

Efficacy results for 127 patients assessed by the IRC are shown in **Table 30**.

Table 30 – Efficacy Results in Study M14-032

Endpoint	IRC Assessment		
	Ibrutinib Failures N = 91	Idelalisib Failures N = 36	All Patients N = 127
ORR, n (%) [95% CI]	64 (70.3) [59.8, 79.5]	25 (69.4) [51.9, 83.7]	89 (70.1) [61.3, 77.9]
CR + CRi, n (%)	1 (1.1)	0	1 (0.8)
nPR, n (%)	0 (0)	0 (0)	0 (0)
PR, n (%)	63 (69.2)	25 (69.4)	88 (69.3)
DOR, % (95% CI)	N = 64	N = 25	N = 89
6-month estimate	96.5 (86.6, 99.1)	100 (100, 100)	97.4 (90.0, 99.4)
12-month estimate	N/A	N/A	N/A
Time to first response, median, months (range)	2.6 (1.0, 8.9)	2.3 (1.6, 5.3)	2.5 (1.0, 8.9)

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

Median DOR has not been reached with DOR for all patients ranging from 0 to 11.6 months with a median follow-up of 18.7 months. The MRD negativity rate in peripheral blood for all 127 patients was 25% (32/127), including 8 patients who achieved MRD negativity in bone marrow.

Study M12-175

Study M12-175 was a Phase 1, multi-center, open-label trial of patients with previously treated CLL, including those with 17p deletion, who had relapsed following or were refractory to standard treatments, and for whom no other therapies were available. Efficacy was evaluated in 67 patients who were administered VENCLEXTA following a dose ramp-up schedule to a final daily dose of 400 mg, and continued to receive 400 mg of VENCLEXTA monotherapy orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months).

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

An overall response rate (ORR) of 71% (95% CI: 58%, 82%), CR + CRi rate of 7% and PR rate of 64% was reported for the 59 patients with relapsed or refractory CLL, as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008).

The DOR ranged from 2.4 to 32.5 months with an estimated median follow up of 9.7 months. The 12-month estimate for DOR was 89% (95% CI: 68%, 98%).

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

VIALE-A (M15-656) was a randomized (2:1), double-blind, placebo controlled Phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine versus placebo in combination with azacitidine in patients with newly diagnosed AML who were ≥ 75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2 or 3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance < 45 mL/min, or other comorbidity.

Patients in VIALE-A completed the 3-day ramp-up schedule to a final 400 mg once daily dose. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. All patients received VENCLEXTA 400 mg orally once daily on Days 1 to 28 plus azacitidine 75 mg/m² either intravenously or subcutaneously on Days 1 to 7 of each 28-day cycle beginning on Cycle 1 Day 1 (see **4 DOSAGE AND ADMINISTRATION**).

Bone marrow assessments were performed at the end of Cycle 1 treatment. If remission was confirmed, defined as less than 5% leukemia blasts, patients with cytopenias had VENCLEXTA or placebo interrupted for up to 14 days or until ANC \geq 500/microL and platelet count \geq 50×10^3 /microL. 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 (see **4 DOSAGE AND ADMINISTRATION**). Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity. Patients continued treatment until disease progression or unacceptable toxicity.

A total of 431 patients were randomized: 286 to the VENCLEXTA + azacitidine arm and 145 to the placebo + azacitidine arm. The baseline demographic and disease characteristics are shown in **Table 31**.

Table 31 – Baseline Demographic and Disease Characteristics in Patients with AML (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; %	1.0	1.4
Asian; %	23	23
Males; %	60	60
ECOG performance status; %		
0 to 1	55	56
2	40	41
3	5.6	3.4
Bone marrow blast; %		
< 30%	30	28
\geq 30% to < 50%	21	23
\geq 50%	49	49
Disease history; %		
<i>De Novo</i> AML	75	76
Secondary AML	25	24
Cytogenetic risk detected^a; %		
Intermediate	64	61
Poor	36	39

Characteristic	VENCLEXTA + Azacitidine N = 286	Placebo + Azacitidine N = 145
Mutation analyses detected; n/N^b (%)		
<i>IDH1 or IDH2</i>	61/245 (25)	28/127 (22)
<i>IDH1</i>	23/245 (9.4)	11/127 (8.7)
<i>IDH2</i>	40/245 (16)	18/127 (14)
<i>FLT3</i>	29/206 (14)	22/108 (20)
<i>NPM1</i>	27/163 (17)	17/86 (20)
<i>TP53</i>	38/163 (23)	14/86 (16)
a. Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.		
b. Number of evaluable bone marrow aspirate specimens received at baseline.		

The dual primary endpoints of the study were overall survival (OS) measured from the date of randomization to death from any cause and composite complete remission rate (complete remission + complete remission with incomplete blood count recovery; CR + CRi) for the first 226 randomized patients with 6 months of follow-up. The overall median follow-up at the time of analysis was approximately 20.5 months (range: < 0.1 to 30.7 months).

VENCLEXTA + azacitidine demonstrated a 34% reduction in the risk of death compared with placebo + azacitidine ($p < 0.001$). The Kaplan-Meier curve for OS is shown in **Figure 4**. The efficacy results are presented in **Table 32**.

Table 32 – Efficacy Results for VIALE-A

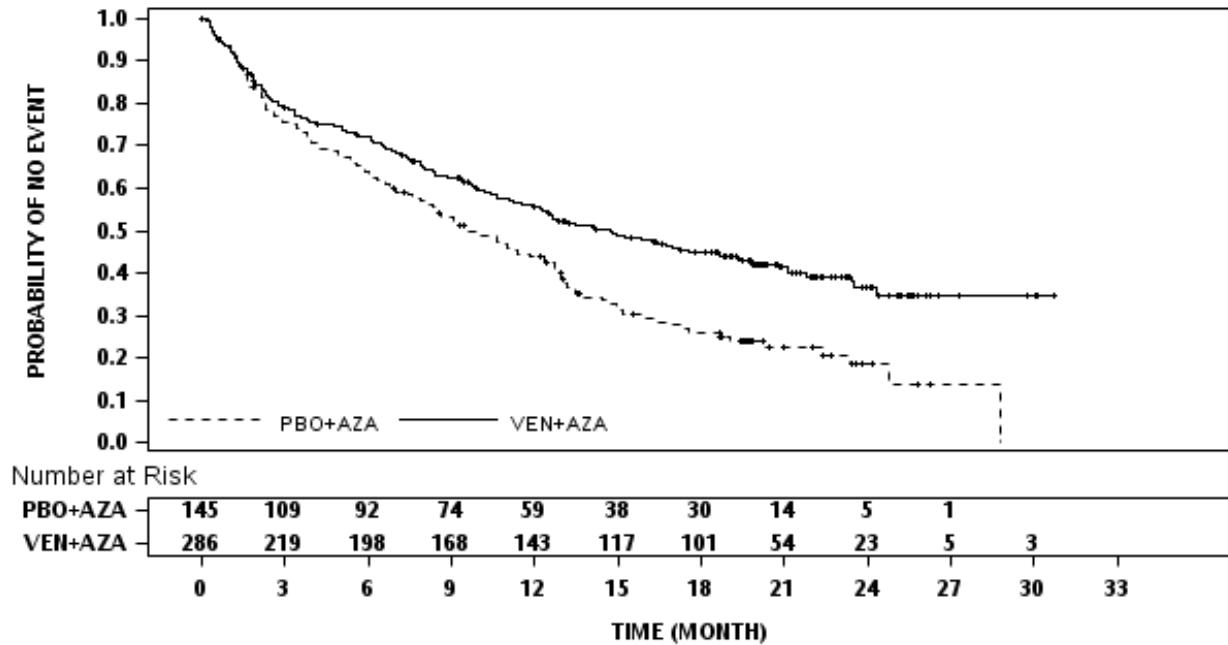
Endpoint	VENCLEXTA + Azacitidine	Placebo + Azacitidine
Overall survival	(N=286)	(N=145)
Number of deaths, n (%)	161 (56)	109 (75)
Median survival ^a , months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
Hazard ratio ^b (95% CI)	0.66 (0.52, 0.85)	
p-value ^b	< 0.001	
CR+CRi^c	(N=147)	(N=79)
n (%)	96 (65)	20 (25)
95% CI	(57, 73)	(16, 36)
p-value ^d	< 0.001	
CR	(N=286)	(N=145)
n (%)	105 (37)	26 (18)

(95% CI)	(31, 43)	(12, 25)
p-value ^d	< 0.001	
Median DOR ^e , months (95% CI)	17.5 (15.3, NR)	13.3 (8.5, 17.6)

CI = confidence interval; NR = not reached.
CR = complete remission, 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; CRi = complete remission with incomplete blood count recovery.

- Kaplan-Meier estimate at the second interim analysis (data cut-off date 04 January 2020).
- Hazard ratio estimate (venetoclax +azacitidine versus placebo + azacitidine) based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18 to < 75, ≥ 75) as assigned at randomization; P-value based on log-rank test stratified by the same factors.
- The CR+CRi rate is from a planned interim analysis of first 226 randomized patients with 6 months of follow-up at the first interim analysis (data cut-off date 01 October 2018).
- P-value is from Cochran-Mantel-Haenszel test stratified by cytogenetics (intermediate risk, poor risk) and age (18 to < 75, ≥ 75) as assigned at randomization.
- DOR (duration of response) was defined as time from first response of CR for DOR of CR, to the first date of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.

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

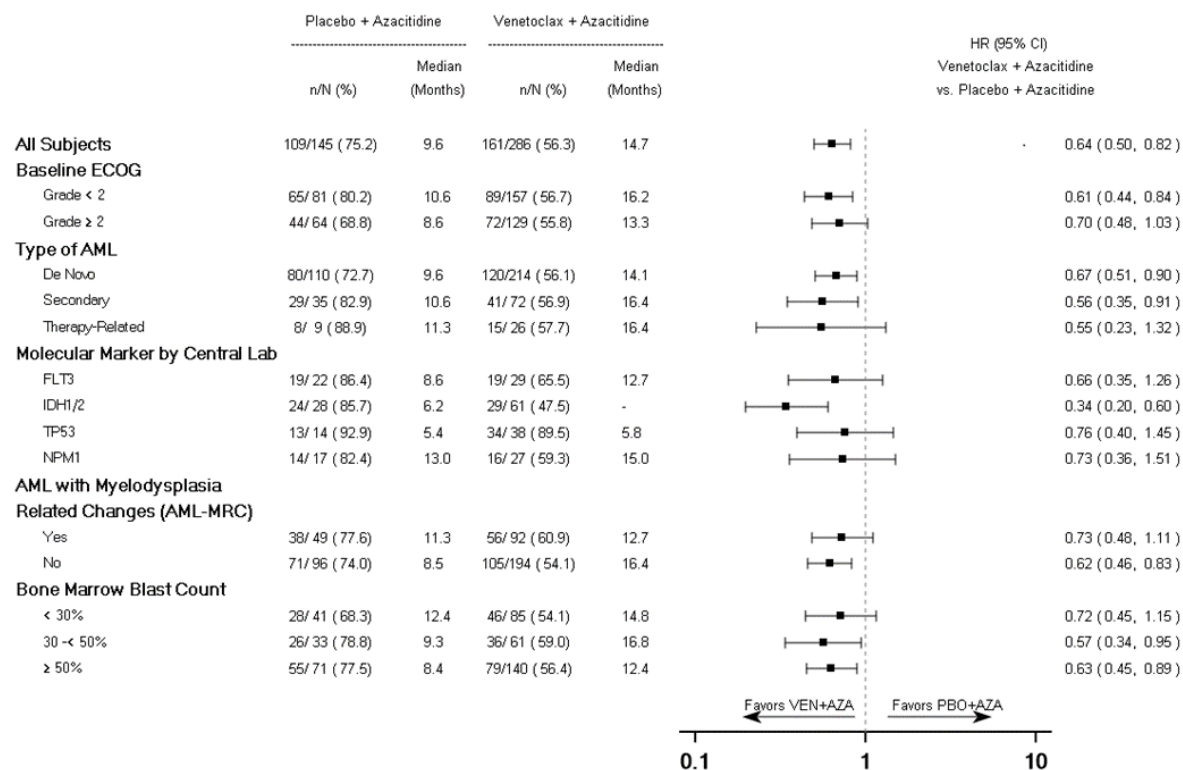


Transfusion independence, defined as a period of ≥ 56 consecutive days with no transfusion after the first dose of study drug, was a pre-defined secondary endpoint. In the VENCLEXTA + azacitidine treatment arm, 155 patients were dependent on red blood cell (RBC) and/or platelet transfusions at baseline; of these patients, 49% (76/155) became independent of RBC and platelet transfusions during any consecutive ≥ 56 -day post-baseline period. There were 131 patients in the VENCLEXTA + azacitidine arm who were independent of both RBC and platelet transfusions at baseline; 69% (90/131) remained transfusion independent. Eighty-one patients treated with placebo + azacitidine were dependent on RBC and/or platelet transfusions at baseline; of these patients, 27% (22/81) became independent of RBC and platelet transfusions during any consecutive ≥ 56 -day post-baseline period. Of the patients treated with placebo + azacitidine, 64 were independent of both RBC and platelet transfusions at baseline; 42% (27/64) remained transfusion independent.

The median time to first response of CR or CRi was 1.3 months (range, 0.6 to 9.9 months) with VENCLEXTA + azacitidine treatment.

In exploratory subgroup analyses, an OS benefit with VENCLEXTA + azacitidine versus placebo + azacitidine treatment was observed across all subgroups examined.

Figure 5 – Forest plot of overall survival by subgroups from VIALE-A



Unstratified hazard ratio (HR) is displayed on the X-axis with logarithmic scale.

'-' = Not reached

VENCLEXTA in Combination With Low-Dose Cytarabine

VIALE-C (M16-043) was a Phase 3 randomized (2:1), double-blind, placebo-controlled, multi-center study that evaluated the efficacy and safety of VENCLEXTA in combination with low-dose cytarabine in patients with newly-diagnosed AML who were ≥ 75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2 or 3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance < 45 mL/min, or other comorbidity.

Patients in VIALE-C completed the 4-day ramp-up schedule to a final 600 mg once daily dose (see **4 DOSAGE AND ADMINISTRATION**). Patients received TLS prophylaxis and were hospitalized for monitoring during the ramp-up period and for at least 24 hours after reaching the final dose of VENCLEXTA on Day 4. All patients received VENCLEXTA 600 mg orally once daily on Days 1 to 28 plus low-dose cytarabine 20 mg/m² subcutaneously (SC) once daily on Days 1 to 10 of each cycle. Placebo orally once daily was administered on Days 1 to 28 plus low-dose cytarabine 20 mg/m² SC once daily on Days 1 to 10.

Bone marrow assessments were performed at the end of Cycle 1 treatment. If remission was confirmed (defined as less than 5% leukemia blasts), patients with cytopenias had VENCLEXTA or placebo interrupted for up to 14 days or until ANC ≥ 500 /microL and platelet count $\geq 25 \times 10^3$ /microL. 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. Low-dose cytarabine was resumed on the same day as VENCLEXTA or placebo following interruption. Patients continued treatment until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

A total of 211 patients were randomized: 143 to the VENCLEXTA + low-dose-cytarabine arm and 68 to the placebo + low-dose cytarabine arm. The baseline demographic and disease characteristics are shown in **Table 33**.

Table 33 – Baseline Demographic and Disease Characteristics in Patients with AML

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
Males; %	55	57

Characteristic	VENCLEXTA + Low-Dose Cytarabine N = 143	Placebo + Low-Dose Cytarabine N = 68
ECOG performance status; %		
0 to 1	52	50
2	44	37
3	4.2	13
Disease history; %		
<i>De Novo</i> AML	59	66
Secondary AML	41	34
Mutation analyses detected; n/N^a (%)		
<i>TP53</i>	22/112 (20)	9/52 (17)
<i>IDH1</i> or <i>IDH2</i>	21/112 (19)	12/52 (23)
<i>FLT3</i>	20/112 (18)	9/52 (17)
<i>NPM1</i>	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.		

The overall median follow-up at the time of the primary analysis was 12 months (range: 0.1 to 17.6 months). Clinical benefit was based on the rate of complete remission (CR) and duration of CR, with supportive evidence of rate of CR + CRi (complete remission with incomplete blood count recovery), duration of CR + CRi and the rate of conversion from transfusion dependence to transfusion independence.

Table 34 – Efficacy Results for VIALE-C

Endpoint	VENCLEXTA + Low-Dose Cytarabine N=143	Placebo + Low-Dose Cytarabine N=68
CR, n, (%)	39 (27)	5 (7)
(95% CI)	(20, 35)	(2, 16)
Median DOR ^a , months (95% CI)	11.1 (5.9, NR)	8.3 (3.1, 8.3)
CR + CRi, n, (%)	68 (48)	9 (13)
(95% CI)	(39, 56)	(6, 24)
Median DOR ^a , months (95% CI)	10.8 (5.9, NR)	6.2 (1.1, NR)
CI = confidence interval; CR + CRi = complete remission + complete remission with incomplete blood count recovery; DOR = duration of response; NR = not reached.		
a. DOR (duration of response) was defined as time from first response of CR for DOR of CR, or from first response of CR or CRi for DOR of CR + CRi, to the first date of confirmed morphologic relapse, or death due to disease progression, whichever occurred earlier. Median DOR from Kaplan-Meier estimate.		

The median time to first response of CR + CRi was 1.1 months (range: 0.8 to 4.7 months) with VENCLEXTA + low-dose cytarabine treatment.

Among the patients treated with VENCLEXTA + low-dose cytarabine, 111 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 33% (37/111) became independent of RBC and platelet transfusions during any consecutive \geq 56-day post-baseline period. There were 32 patients in the VENCLEXTA + low-dose cytarabine arm who were independent of both RBC and platelet transfusions at baseline; 50% (16/32) remained transfusion independent of both RBC and platelet transfusions during any consecutive \geq 56-day post-baseline period.

Among the patients treated with placebo + low-dose cytarabine 55 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 13% (7/55) patients became independent of RBC and platelet transfusions during any consecutive \geq 56-day post-baseline period. Of the patients treated with placebo + low-dose cytarabine, 13 were independent of both RBC and platelet transfusions at baseline, 31% (4/13) remained transfusion independent during any consecutive \geq 56-day post-baseline period.

VENCLEXTA + low-dose cytarabine did not significantly improve overall survival (OS) versus placebo + low-dose cytarabine. The hazard ratio (HR) for OS was 0.75 (95% CI: 0.52, 1.07); p-value 0.114. The median OS for the VENCLEXTA + low-dose cytarabine arm was 7.2 months (95% CI: 5.6, 10.1) and for placebo + low-dose cytarabine arm was 4.1 months (95% CI: 3.1, 8.8).

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Long-Term Toxicity

Repeated dose toxicity studies were conducted up to 26 weeks in duration in mice and up to 39 weeks in dogs. Dose-dependent reductions in lymphocytes and red blood cell mass were observed in animal studies with venetoclax. Both effects were reversible after cessation of dosing with venetoclax, with recovery of lymphocytes occurring by 18 weeks post treatment. Both B- and T-cells were affected, but the most significant decreases occurred with B-cells. Decreases in lymphocytes were not associated with opportunistic infections.

In dogs, venetoclax also caused single-cell necrosis in various tissues, including the gallbladder and exocrine pancreas, 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 the 9-month study, these changes were observed at the lowest dose of 2 mg/kg/day (0.5 times the human AUC at 400 mg/day).

After approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair. In the 9-month study, these changes occurred at doses \geq 6 mg/kg/day (1.5 times the human AUC at 400 mg/day). No changes in the quality of the hair coat or skin were observed, nor in other pigmented tissues examined (e.g., the iris and the ocular fundus of the eye). Reversibility of the hair coat changes has not been assessed in dogs.

Carcinogenicity and Mutagenicity

Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax and at a single dose level of 250 mg/kg/day of M27. Exposure margins (AUC), relative to the clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for 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.

Reproductive and Developmental Toxicology

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluated 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 (in male and female mice, approximately 2.8 and 3.2 times the human AUC exposure at the recommended dose of 400 mg/day, respectively). However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at all dose levels examined (0.5 times the human AUC exposure at the recommend dose of 400 mg/day). Testicular germ cell depletion was not reversible following 4 weeks of once daily oral dosing and a 4-week non-dosing recovery period. Reversibility over longer recovery periods has not been assessed.

In embryo-fetal development studies, VENCLEXTA was administered to pregnant mice and rabbits to evaluate potential effects after implantation and subsequent embryo-fetal development during the respective periods of organogenesis. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at the recommended dose of 400 mg/day). In rabbits, VENCLEXTA at 300 mg/kg/day produced maternal toxicity, but no fetal toxicity (maternal exposures approximately 0.2 times the human AUC exposure at the recommended dose of 400 mg/day). No teratogenicity was observed in either the mouse or the rabbit.

In a juvenile toxicology study, mice were administered VENCLEXTA 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, hunched posture, abdominal distention, and brown fur staining 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, which were consistent with adult mice and considered non-adverse.

The venetoclax No Observed Adverse Effect Level (NOAEL) of 10 mg/kg/day in mice is approximately 0.14 times the clinical dose of 400 mg on a mg/m² basis.

Phototoxicity

Venetoclax absorbs light within the range of natural sunlight. There was no evidence of cutaneous phototoxicity in hairless mice that received up to 825 mg/kg/day once daily for 3 days. Systemic exposure to venetoclax in this study cannot be confirmed. In rats, there was no evidence that [¹⁴C]-venetoclax-derived radioactivity selectively associates with tissues containing melanin.

17 SUPPORTING PRODUCT MONOGRAPHS

1. GAZYVA® 25 mg/mL Concentrate for Solution for Infusion, Submission Control No. 208089, Product Monograph, Hoffmann-La Roche Limited (August 9, 2018)
2. RITUXAN® 10 mg/mL Intravenous Infusion, Submission Control No. 228891, Product Monograph, Hoffmann-La Roche Limited (October 10, 2019)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

P^rVENCLEXTA[®]

venetoclax tablets

Read this carefully before you start taking **VENCLEXTA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VENCLEXTA**.

Serious Warnings and Precautions

VENCLEXTA should only be prescribed by a doctor who is experienced in the use of anti-cancer drugs.

VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program. The Starting Pack is meant for patients with Chronic Lymphocytic Leukemia (CLL).

VENCLEXTA can cause the following 2 serious side effects:

- Tumour lysis syndrome (TLS).

To reduce your risk of TLS:

- You will start taking VENCLEXTA at a low dose. Your dose will be increased slowly up to the full dose:
 - Each week for 5 weeks, if you are taking VENCLEXTA for your CLL.
 - Each day for 3 days, if you are taking VENCLEXTA with azacitidine for your Acute Myeloid Leukemia (AML).
 - Each day for 4 days, if you are taking VENCLEXTA with low-dose cytarabine for your AML.
- If you have CLL, your doctor will do blood tests during the first 5 weeks to check for TLS.
- If you have AML, your doctor will do blood tests during the first week to check for TLS.
- You will need to drink plenty of water. You may need to receive intravenous fluids at an outpatient clinic or hospital on specific days during the first 5 weeks if you have CLL, or 3 to 4 days if you have AML. You will also receive other medicines before starting VENCLEXTA to reduce your risk of TLS.
- Do not take any medicines that may have a strong interaction with VENCLEXTA.
- Sepsis (a blood infection in the entire body).

Some patients need to go to the hospital or may die from sepsis. Your doctor will closely monitor and treat you.

What is VENCLEXTA used for?

Chronic Lymphocytic Leukemia (CLL):

VENCLEXTA is used to treat adults with CLL. It is taken:

- **with another drug called obinutuzumab.** This is used when CLL has not been treated before.

Or

- **with another drug called rituximab.** This is used when CLL has come back or has not responded to treatment.

Or

- **by itself** when CLL:
 - has a chromosome deletion and has come back or has not responded to treatment; or
 - has no chromosome deletion and other treatments are not available.

CLL is a type of cancer that affects the lymph nodes and white blood cells called “B lymphocytes”. In CLL, unhealthy B lymphocytes multiply too quickly and live for too long. This causes there to be too many of them in the blood.

Acute Myeloid Leukemia (AML):

VENCLEXTA is used to treat adults with AML:

- whose disease has not been treated before, and
- who are at least 75 years of age or have medical conditions that prevent them from having other types of chemotherapy.

For these patients, VENCLEXTA is taken with another drug. This could be either azacitidine or low-dose cytarabine.

AML is a cancer of the bone marrow and the blood. It affects white blood cells that are not fully developed called myeloid blasts. In AML, there are changes in the myeloid blasts that stop them from becoming mature blood cells. These immature blasts build up in the bone marrow and blood. This blocks normal cells from being produced and causes there to be lower number of healthy blood cells.

How does VENCLEXTA work?

VENCLEXTA works by blocking a protein in the body called “BCL-2”. This is a protein that helps cancer cells survive. Blocking this protein helps to kill and lower the number of cancer cells.

What are the ingredients in VENCLEXTA?

Medicinal ingredient: venetoclax

Non-medicinal ingredients: calcium phosphate dibasic, colloidal silicon dioxide, copovidone, iron oxide yellow, polyethylene glycol, polysorbate 80, polyvinyl alcohol, sodium stearyl fumarate, talc and titanium oxide

The 50 mg tablet also contains iron oxide black and iron oxide red.

VENCLEXTA comes in the following dosage forms:

Tablets: 10 mg, 50 mg, and 100 mg

Do not use VENCLEXTA if:

- you are allergic to venetoclax or to any of the other ingredients in VENCLEXTA or to any part of the container.
- you have CLL and are taking certain medicines when you start your treatment and during the time when your dose is gradually being increased (usually over 5 weeks). This is because these medicines may have a strong interaction with VENCLEXTA. Some of these medicines include:
 - clarithromycin, used for bacterial infections
 - itraconazole, ketoconazole, posaconazole or voriconazole, used for fungal infections
 - ritonavir, used for HIV infection

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VENCLEXTA. Talk about any health conditions or problems you may have, including if you:

- have low levels of neutrophils (a type of white blood cell), which is called neutropenia
- have kidney or liver problems
- have any signs or symptoms of infection such as fever, chills, cough, feeling weak or confused, or a painful or burning feeling when passing urine
- have recently received or are scheduled to receive a vaccine

Other warnings you should know about:

Bleeding problems

If you are a patient with AML and are taking VENCLEXTA with azacitidine or low-dose cytarabine, you may be at higher risk for serious bleeding problems. These bleeding problems could lead to death. Your healthcare professional will monitor you for signs of bleeding problems.

Other cancers

During treatment with VENCLEXTA, a higher number of cases of certain types of non-melanoma skin cancer have been reported. Your healthcare professional will monitor you for the signs of skin cancer.

Tumour lysis syndrome

VENCLEXTA can cause a serious side effect called tumour lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. As cancer cells are destroyed, they release their contents, leading to high levels of certain chemicals (potassium, uric acid, phosphorus) and low levels of calcium in the blood. High or low levels of these chemicals can cause serious damage to your kidneys or other organs and may lead to death. TLS is most likely to occur in the first days or weeks of treatment with VENCLEXTA, as you increase your dose. It can also happen if you need to stop and restart your treatment.

If you have a higher number of cancer cells in your body, kidney problems, or an enlarged spleen, your risk for TLS may be higher. The changes in your blood that could lead to TLS may have no symptoms. Having your blood tested is important in order to treat and prevent TLS. The symptoms below can be associated with rapid cell death or TLS:

- fever
- chills
- nausea (feeling sick to your stomach)
- vomiting
- confusion
- shortness of breath
- seizure
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle pain
- joint discomfort

If you notice any of these, call your doctor or nurse right away.

If you have CLL:

- Your doctor will do tests to check your risk of getting TLS before you start taking VENCLEXTA. Your doctor will also do blood tests during your first 5 weeks of treatment to check for TLS. It is important to keep your scheduled appointments for blood tests.
- Your doctor will give you other medicines before starting and during treatment with VENCLEXTA to help reduce your risk of TLS.

- You will need to drink plenty of water when taking VENCLEXTA to help reduce your risk of getting TLS.
 - For patients with CLL, follow the instructions about drinking water in the Quick Start Guide and as labelled inside the weekly wallet blister packs.
- Your doctor may hospitalize you before you start VENCLEXTA to give intravenous (IV) fluids into your vein, do blood tests, and check for TLS.

If you have AML:

- Your doctor may hospitalize you before you start your treatment. You may remain in hospital until 24 hours after you have reached the full VENCLEXTA dose. This will allow your healthcare professional to:
 - make sure that you have enough water/fluids,
 - give you medicines to prevent the build-up of uric acid in your body, and
 - do blood tests before you start to take VENCLEXTA, while they increase your dose and when you start to take the full dose.

Adults 65 years of age and older:

Adults 65 years of age and older may be more likely to experience certain side effects when taking VENCLEXTA in combination with other medicinal products.

Children and adolescents less than 18 years of age:

It is not known if VENCLEXTA is safe or will work in children or adolescents less than 18 years of age.

Pregnancy, breastfeeding, birth control and fertility:

- VENCLEXTA should not be used during pregnancy. It may harm your unborn baby. Tell your doctor immediately if you become pregnant.
- Women who are able to become pregnant should have a pregnancy test before starting treatment with VENCLEXTA and should use effective birth control during treatment with VENCLEXTA and for at least 30 days after stopping treatment.
- Do not breastfeed while you are taking this medicine.
- VENCLEXTA may cause male infertility (low or no sperm count). This may affect your ability to father a child. Ask your doctor for advice before starting treatment with VENCLEXTA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VENCLEXTA:

- some medicines used to treat fungal infections – like fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole
- some medicines used to treat bacterial infections – like ciprofloxacin, clarithromycin, erythromycin, nafcillin and rifampin
- some medicines used to prevent seizures or to treat epilepsy – like carbamazepine and phenytoin
- some medicines used to treat HIV infection – like efavirenz, etravirine, and ritonavir
- some medicines used to treat high blood pressure or heart-related chest pain (angina) – like bosentan, captopril, carvedilol, diltiazem, felodipine, ranolazine and verapamil
- a medicine used to treat a sleep disorder (narcolepsy) known as modafinil
- some herbal medicines – like St John’s wort and quercetin
- a blood thinner known as warfarin
- some medicines used to treat heart conditions – like amiodarone, digoxin, quinidine and ticagrelor
- an immunosuppressant drug known as cyclosporine
- DO NOT eat grapefruit (or drink its juice), Seville oranges (or marmalades) or starfruit while you are taking VENCLEXTA. These products may increase the amount of VENCLEXTA in your blood.

How to take VENCLEXTA:

- Always take VENCLEXTA exactly as your doctor tells you.
- Drink plenty of water when taking VENCLEXTA to help reduce your risk of getting TLS.
- Take the tablets with a meal and water at the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break the tablets.
- Your doses of VENCLEXTA may be lower in some cases, including if:
 - you have severe liver problems, or
 - you are taking certain medicines that can interact with VENCLEXTA.
- Your treatment may be interrupted or your dose lowered if you experience certain side effects.

For patients with CLL:

When starting VENCLEXTA:

- Read the Quick Start Guide that comes with your Starting Pack (which contains 4 weekly wallet blister packs).
- Drink 7 glasses of water each day (1.75 litres total). Start drinking this amount of water 2 days before your first dose. Continue to drink this amount each day. This is especially important on the 2 days leading up to your first dose and every time your dose is increased (days 1, 6 and 7 of each week). Follow the instructions about drinking water in the Quick Start Guide and as labelled inside the weekly wallet blister packs.
- Your doctor will do required blood testing prior to starting each week of the Starting Pack, as well as 6 to 8 hours and 24 hours after your first dose for each of the first 2 weeks of VENCLEXTA treatment. Do not take your next dose until your doctor knows the results of these blood tests and tells you it is safe to do so.
- Do not start a new dose unless your doctor tells you it is safe to do so.

Usual dose:

Your doctor will start VENCLEXTA at a low dose for 1 week. Your doctor will gradually increase the dose over the next 4 weeks to the full standard dose.

The usual dose is as follows:

- The starting dose is 20 mg (two 10 mg tablets) once a day for 7 days.
- The dose will be increased to 50 mg (one 50 mg tablet) once a day for 7 days.
- The dose will be increased to 100 mg (one 100 mg tablet) once a day for 7 days.
- The dose will be increased to 200 mg (two 100 mg tablets) once a day for 7 days.
- The dose will be increased to 400 mg (four 100 mg tablets) once a day.
 - If you are taking VENCLEXTA alone, you will stay on the 400 mg daily dose, which is the standard dose, for as long as necessary.
 - If you are taking VENCLEXTA in combination with rituximab:
 - You will start your rituximab after the first 5 weeks of VENCLEXTA.
 - You will receive VENCLEXTA for 2 years.
 - If you are taking VENCLEXTA in combination with obinutuzumab:
 - You will start VENCLEXTA dosing after receiving your first cycle of obinutuzumab doses.
 - You will receive VENCLEXTA for 12 months.

For patients with AML:

- Your healthcare professional will do blood tests before you start taking VENCLEXTA. Blood tests will be repeated regularly throughout your treatment.
- Your healthcare professional will ensure that you are well hydrated during the time when your dose is being increased. They may also give you other medicines to help prevent side effects during this time.

Usual dose for VENCLEXTA in combination with azacitidine:

Your doctor will start VENCLEXTA at a low dose. Your doctor will gradually increase the dose over the next 3 days to the full dose.

The usual dose is as follows:

- The starting dose is 100 mg (one 100 mg tablet) once a day for 1 day.
- The dose will be increased to 200 mg (two 100 mg tablets) once a day for 1 day.
- The dose will be increased to 400 mg (four 100 mg tablets) once a day for 1 day.
- You will continue to take 400 mg (four 100 mg tablets) per day for as long as necessary. This is the standard dose.

You will start your azacitidine on the same day that you start VENCLEXTA.

Usual dose for VENCLEXTA in combination with low-dose cytarabine:

Your doctor will start VENCLEXTA at a low dose. Your doctor will gradually increase the dose over the next 4 days to the full dose.

The usual dose is as follows:

- The starting dose is 100 mg (one 100 mg tablet) once a day for 1 day.
- The dose will be increased to 200 mg (two 100 mg tablets) once a day for 1 day.
- The dose will be increased to 400 mg (four 100 mg tablets) once a day for 1 day.
- The dose will be increased to 600 mg (six 100 mg tablets) once a day.
- You will continue to take 600 mg (six 100 mg tablets) per day for as long as necessary. This is the standard dose.

You will start your cytarabine on the same day that you start VENCLEXTA.

If you have questions about your dose of VENCLEXTA, talk to your healthcare professional.

Overdose:

If you think you have taken too much VENCLEXTA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

- If it has been less than 8 hours, take your dose as soon as possible.
- If it has been more than 8 hours, skip the missed dose and take the next dose at your usual time the next day.
- If you vomit after taking VENCLEXTA, do not take an extra dose. Take the next dose at your usual time the next day.
- If you are not sure, talk to your healthcare professional.

What are possible side effects from using VENCLEXTA?

These are not all the possible side effects you may feel when taking VENCLEXTA. If you experience any side effects not listed here, contact your healthcare professional.

- diarrhea or constipation
- nausea
- vomiting
- decreased appetite
- weight loss
- stomach pain
- swelling of your arms, legs, hands and feet
- weakness
- mouth sores
- shortness of breath
- rash
- fever
- headache
- dizziness
- feeling tired

- cough
- muscle, back, bone, neck and joint pain
- itching

VENCLEXTA may cause abnormal exam and blood test results. Your doctor will do some tests before and during your treatment. The doctor will interpret the results. They will tell you if there are any abnormalities in your tests that might need treatment.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Leukopenia, Neutropenia, Lymphopenia (low levels of white blood cells): any signs of infection such as fever, chills, sweating, aches, pains, fatigue and flu-like symptoms		✓	
Anemia (low levels of red blood cells): fatigue, pale skin, shortness of breath, weakness		✓	
Thrombocytopenia (low levels of blood platelets): increases risk of bleeding or bruising		✓	
Sepsis and septic shock (a blood infection in the entire body): fever or dizziness, chills, high or very low body temperature, feel weak, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat			✓
COMMON			
Hemorrhage (bleeding problems): blood in stool, urine or eyes; vomiting blood; sudden and severe headache; nose bleeds; coughing up blood; purple spotted rash on the skin			✓
Hyperkalemia (high potassium levels in the blood): muscle fatigue, weakness, irregular heartbeat, nausea		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Pneumonia (infection of the lungs): chills, cough with or without mucus, fever, shortness of breath		✓	
Respiratory tract infection: runny nose, sore and scratchy throat, cough, sneezing, weak or loss of voice		✓	
Urinary tract infection: burning sensation during urination, low urine output despite feeling urge to urinate more often, pain in the pelvis or lower back, cloudy urine that may contain blood		✓	
RARE			
Tumour lysis syndrome (TLS): chills, confusion, dark or cloudy urine, fever, irregular heartbeat, joint discomfort, muscle pain, nausea, shortness of breath, seizure, tiredness, vomiting			✓
Multi-organ Dysfunction Syndrome (failure of multiple organs): failure of multiple organs (e.g., lung, kidney, heart) at the same time including passing less urine, difficulty breathing (including shortness of breath at rest or with activity), rapid breathing, wheezing or cough; yellowing of your skin and eyes, stomach pain or swelling, nausea or vomiting; chest pain (angina), shortness of breath, rapid, strong or irregular heartbeat, or if there is swelling of your ankles or feet			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2 and 30°C.

Keep out of reach and sight of children.

Access to VENCLEXTA

VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program. Talk to your doctor for more information.

If you want more information about VENCLEXTA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>), the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

Last Revised: APR 05, 2022