PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVENCLEXTA®

venetoclax tablets
10 mg, 50 mg and 100 mg

Other Antineoplastic Agent

Date of Preparation:
September 27, 2016

Date of Previous Revision:
December 02, 2019

Date of Revision:
January 13, 2020

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Submission Control No: 224252

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VENCLEXTA

venetoclax tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
oral	tablets: 10 mg, 50 mg and 100 mg	For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

INDICATIONS AND CLINICAL USE

VENCLEXTA in Combination with Rituximab

VENCLEXTA (venetoclax) in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

VENCLEXTA as Monotherapy

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 is based on response rate results from single-arm studies (see **CLINICAL TRIALS**).

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

Pediatrics (< 18 years of age):

No safety and efficacy data for VENCLEXTA in children and adolescents below 18 years of age are available.

Geriatrics (≥ 65 years of age):

No overall differences in safety and effectiveness were observed between older and younger patients in the combination (MURANO) and the monotherapy studies (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- Concomitant use of VENCLEXTA (venetoclax) with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

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 **Endocrine and Metabolism**).
    - Weekly dosage ramp-up over a period of 5 weeks, with blood chemistry monitoring on each dose ramp-up is required (see **DOSAGE AND ADMINISTRATION**).
    - Patients must receive prophylaxis for TLS, including hydration and anti-hyperuricemics prior to initiating treatment (see **DOSAGE AND ADMINISTRATION**).
    - Concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.
- Serious infections that may lead to hospitalization or death (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Carcinogenesis and Mutagenesis

Second Primary Malignancies

In the VENCLEXTA combination study (MURANO), second primary malignancies were more frequently reported with VENCLEXTA + rituximab (11%) than bendamustine plus rituximab (7%). The higher reporting rate in the VENCLEXTA plus rituximab arm was primarily due to the higher frequency of non-melanoma skin malignancies (7% versus 3% in the bendamustine plus 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 with previously treated CLL with high tumour burden when treated with VENCLEXTA (see **ADVERSE REACTIONS**).

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. 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 **Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION)**.

The risk of TLS is a continuum based on multiple factors, including tumour burden (see **Table 6**) and comorbidities. Reduced renal function (creatinine clearance [CrCl] < 80 ml/min) further increases the risk. Patients should be assessed for risk and all patients 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 **Monitoring and Laboratory Tests**). Interrupt dosing until any identified laboratory abnormalities are resolved. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases (see **DOSAGE AND ADMINISTRATION**).

Venetoclax is a CYP3A and P-gp substrate. Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors increases venetoclax exposure and increases the risk of TLS at initiation and during ramp-up phase (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.

Avoid concomitant use of moderate CYP3A inhibitors and P-gp inhibitors at initiation and during the ramp-up phase. Consider alternative treatments. If concomitant use of a moderate CYP3A inhibitor or P-gp inhibitor is necessary, reduce the VENCLEXTA dose by at least 50% and monitor patients more closely for signs of VENCLEXTA toxicities (see **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

Neutropenia

Neutropenia is an identified risk with VENCLEXTA treatment.

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 **ADVERSE REACTIONS**).

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 **DOSAGE AND ADMINISTRATION**).

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 **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 **DOSAGE AND ADMINISTRATION**).

In the MURANO study, 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 1**). Serious infections were reported in 21% of patients treated with VENCLEXTA + rituximab including four fatal cases (three died from pneumonia and one from sepsis) compared with 24% of patients treated with bendamustine + rituximab including four fatal cases (two sepsis and one case each of scedosporium infection and Listeria sepsis).

In the pooled VENCLEXTA 400 mg monotherapy safety database, 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.

Renal

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 (CrCl ≥ 30 mL/min and < 90 mL/min) based on the results of the population pharmacokinetic analysis (see **ACTION AND CLINICAL PHARMACOLOGY**). A recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis.

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

Sexual Function/Reproduction

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.

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 **TOXICOLOGY**).

Special Populations

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 **TOXICOLOGY**).

Nursing Women

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

Breastfeeding should be discontinued during treatment with VENCLEXTA.

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.

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 the combination study with rituximab and the monotherapy studies. In the combination study (MURANO), 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.

Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment based on the results of the population pharmacokinetic analysis (see **ACTION AND CLINICAL PHARMACOLOGY**). These patients should be monitored more closely for signs of toxicity at initiation and during the dose ramp-up phase (see **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 **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

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 mg 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 **Endocrine and Metabolism**) this same monitoring schedule should be performed when starting each subsequent ramp-up. Refer to **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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

VENCLEXTA in Combination with Rituximab

The safety of VENCLEXTA (venetoclax) 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 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 (≥ 20%) of any Grade with 5% higher frequency reported in the VENCLEXTA + rituximab arm were neutropenia, diarrhea, and upper respiratory tract infection. Grade 3-4 adverse events were reported more frequently in the VENCLEXTA plus rituximab arm than in the bendamustine plus rituximab arm (64% vs. 48%), mainly due to Grade 3-4 neutropenia (see **Table 1**).

Serious adverse reactions were reported in 46% of patients treated with VENCLEXTA + rituximab. The most frequently (≥ 2%) reported serious adverse reactions in the VENCLEXTA + rituximab arm were pneumonia, febrile neutropenia, pyrexia, and tumour lysis syndrome. Deaths due to adverse event were reported in ten 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 modification 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 (≥ 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 (≥ 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.

Tumour Lysis Syndrome

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

VENCLEXTA in Combination with Rituximab

In the combination study (MURANO), 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 **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 **DOSAGE AND ADMINISTRATION**). Common treatment-emergent laboratory abnormalities identified in the MURANO trial are presented in **Table 2**.

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 **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 4**).

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

VENCLEXTA in Combination with Rituximab

Table 1 provides the adverse reactions reported in MURANO.

Table 1. Summary of Adverse Reactions Reported with Incidence of ≥ 10% and ≥ 5% Higher for all Grades or ≥ 2% Higher for Grade 3 or 4 in Patients Treated with VENCLEXTA Plus Rituximab Compared with Bendamustine Plus Rituximab

	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
Adverse Reaction by Body System	**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

	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
Adverse Reaction by Body System	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
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

a. Includes the following preferred terms: Neutropenia and neutrophil count decreased.

b. Includes the following preferred terms: laryngitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, upper respiratory tract infection, and viral upper respiratory tract infection.

c. Includes the following preferred terms: bronchitis, bronchitis chronic, lower respiratory tract infection, and lung infection.

d. Includes the following preferred terms: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

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).

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

Blood & 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%)

Respiratory, thoracic and mediastinal disorders: cough (18%)

Infections & 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%).

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

Laboratory Abnormalities

Table 2 provides common laboratory abnormalities reported in MURANO.

Table 2. Common (≥ 10%) New or Worsening Laboratory Abnormalities[a] Occurring at ≥ 5% (Any Grade) or ≥ 2% (Grade 3 or 4) Higher Incidence with VENCLEXTA plus Rituximab Compared with Bendamustine plus Rituximab

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

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

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.

VENCLEXTA as Monotherapy

Adverse reactions described in **Table 3** 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 3. Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade 3 or 4) of Patients with Previously Treated CLL

	VENCLEXTA (N = 352)	
Adverse Reaction by Body System	**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
Nervous system disorders		
Headache	18.8	0.6
Dizziness[m]	14.8	0

	VENCLEXTA (N = 352)	
Adverse Reaction by Body System	**Any Grade (%)**	**Grade 3 or 4 (%)**
Metabolism and nutrition disorders[n]		
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

a. Neutropenia/neutrophil count decreased.

b. Anaemia/haemoglobin decreased.

c. Thrombocytopenia/platelet count decreased

d. Lymphopenia/lymphocyte count decreased.

e. Includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper

f. Includes mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, and stomatitis

g. Includes asthenia, fatigue, and lethargy

h. Includes face oedema, fluid overload, oedema peripheral, peripheral swelling, and generalized oedema.

i. Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, upper respiratory tract infection, and viral upper respiratory tract infection.

j. Includes atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia legionella, pneumonia fungal, pneumonia respiratory syncytial viral, pneumonia viral.

k. Includes bronchitis, bronchitis chronic, lower respiratory tract infection, lung infection.

l. Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

m. Includes dizziness and vertigo.

n. Rates are based on all patients treated with venetoclax 400mg once daily and therefore differ from those presented in **Table 4** which only includes patients who followed the current dose ramp-up schedule and TLS prophylaxis measures.

o. Hyperphosphataemia/blood phosphorus increased.

p. Hypokalemia/blood potassium decreased.

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.

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

Infections & 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 **DOSAGE AND ADMINISTRATION** are presented in **Table 4.**

Table 4. Adverse Reactions Relevant to TLS Reported in Patients with Previously Treated CLL

	VENCLEXTA (N = 168)	
Adverse Reaction	**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.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Table 5 provides common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 5. 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.

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of VENCLEXTA (venetoclax) with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see below).

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.

Drug-Drug Interactions

Effect of Other Drugs on VENCLEXTA

CYP3A Inhibitors

Co-administration of ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Co-administration of 50 mg once daily ritonavir, a strong CYP3A, P-gp and OATP1B1/B3 inhibitor, for 14 days in 6 healthy subjects increased venetoclax C_{max} by 2.4-fold and AUC by 7.9-fold. Concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) is contraindicated at initiation and during ramp-up phase.

Avoid concomitant use of moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) with VENCLEXTA at initiation and during ramp-up phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the initiation and ramp-up doses of VENCLEXTA by at least 50%. Monitor patients more closely for signs of VENCLEXTA toxicities (see **DOSAGE AND ADMINISTRATION)**.

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

For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 50% when used concomitantly with moderate CYP3A inhibitors and by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor (see **DOSAGE AND ADMINISTRATION**).

P-gp Inhibitors

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

Avoid concomitant use of P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) with VENCLEXTA at initiation and during ramp-up phase. Consider alternative treatments. If a P-gp inhibitor must be used, reduce the initiation, ramp-up and steady daily doses of VENCLEXTA by at least 50%. Monitor patients more closely for VENCLEXTA toxicities (see **DOSAGE AND ADMINISTRATION**).

Azithromycin

Co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days in 12 healthy subjects decreased venetoclax C_{max} and AUC_{∞} by 25% and 35%, respectively. No dose adjustment is needed when venetoclax is co-administered with azithromycin.

CYP3A Inducers

Co-administration of once daily rifampin, a strong CYP3A inducer, decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

Effects of VENCLEXTA on Other Drugs

P-gp and BCRP Substrates

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. In a drug-drug interaction study in 10 healthy subjects, administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin C_{max} and a 9% increase in digoxin AUC_{∞}.

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

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

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 **ACTION AND CLINICAL PHARMACOLOGY**). VENCLEXTA should be administered with a meal.

Drug-Herb Interactions

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

Drug-Lifestyle 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Instruct patients to take VENCLEXTA (venetoclax) 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.

Risk Assessment and Prophylaxis for Tumour Lysis Syndrome

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.

The risk of TLS is a continuum based on multiple factors, including tumour burden and comorbidities. Reduced renal function (CrCl < 80 ml/min) further increases the risk. The risk may decrease as tumour burden decreases with VENCLEXTA treatment (see **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 mg 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 6**).

Table 6 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

Table 6. 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 • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg 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 • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion • Consider hospitalization for patients with CrCl < 80ml/min at first dose of 20 mg 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 mg 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.

a. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.

c. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

d. For patients at continued risk of TLS (based on residual, tumour burden, observed laboratory changes consistent with tumour lysis, or comorbidities, see **WARNINGS AND PRECAUTIONS**), monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Recommended Dose and Dosage Adjustment

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 7**. The 5-week ramp-up dosing schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of TLS.

Table 7. Dosing Schedule for Ramp-Up Phase

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 **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the ramp-up schedule with VENCLEXTA and has received the 400 mg dose of VENCLEXTA for 7 days (see **Table 7**). In the MURANO study, rituximab was administered to patients at 375 mg/m^2 intravenous (IV) on Day 1 of Cycle 1 followed by 500 mg/m^2 on Day 1 of Cycles 2 through 6 for a total of six infusions of rituximab (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.

VENCLEXTA as 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.

Dose Modifications Based on Toxicities

Dosing interruption and/or dose reduction may be required. 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.

Dose Modification for Tumour Lysis Syndrome

If a patient experiences blood chemistry changes suggestive of TLS, withhold the following day's VENCLEXTA dose. If resolved within 24 to 48 hours of last dose, resume treatment with VENCLEXTA at the same dose.

For any events of clinical TLS, or for blood chemistry changes requiring more than 48 hours to resolve, resume treatment at a reduced dose (see **Table 8**). When resuming treatment with VENCLEXTA after interruption due to TLS, follow the instructions for Prophylaxis for Tumour Lysis Syndrome.

Dose Modification for Other Toxicities

Withhold VENCLEXTA treatment for any Grade 3 or 4 non-hematological toxicities, Grade 3 neutropenia with infection or fever, or Grade 4 hematological toxicities, except lymphopenia. To reduce the infection risks associated with neutropenia, G-CSF may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, therapy with VENCLEXTA may be resumed at the same dose.

If the toxicity recurs, and for any subsequent occurrences, follow the dose reduction guidelines in **Table 8** when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.

For patients who require dose reductions to less than 100 mg for more than 2 weeks, consider discontinuing VENCLEXTA.

Table 8. Dose Reduction for Toxicity During VENCLEXTA Treatment

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 for Patients with Hepatic and Renal 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 closely for signs of toxicity (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

No dose adjustment is recommended for patients with mild or moderate renal impairment (CrCl $\geq$ 30 mL/min). A recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Dose Modifications for Use with CYP3A Inhibitors/Inducers

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during ramp-up phase. Concomitant use of VENCLEXTA with strong CYP3A inhibitors is contraindicated at dose initiation and during ramp-up phase.

Avoid concomitant use of moderate CYP3A inhibitors with VENCLEXTA at initiation and during ramp-up phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the initiation and ramp-up doses of VENCLEXTA by at least 50%. Monitor patients more closely for signs of toxicities (see **DOSAGE AND ADMINISTRATION**).

For patients who have completed the ramp-up phase and are on steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 50% when used concomitantly with moderate CYP3A inhibitors and by at least 75% when used concomitantly with strong CYP3A inhibitors. Monitor patients more closely for toxicities. Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor (see **DOSAGE AND ADMINISTRATION**).

Dose Modifications for Use with P-gp Inhibitors

Concomitant use of VENCLEXTA with P-gp inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and during ramp-up phase.

Avoid concomitant use of P-gp inhibitors with VENCLEXTA at initiation and during ramp-up phase. Consider alternative treatments. If a P-gp inhibitor must be used, reduce the initiation, ramp-up and steady daily doses of VENCLEXTA by at least 50%. Monitor patients more closely for signs of toxicities.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 tumour lysis syndrome 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.

ACTION AND CLINICAL PHARMACOLOGY

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.

Mechanism of Action

Venetoclax binds to the BH3-binding groove of BCL -2, displacing pro-apoptotic proteins like BIM to initiate mitochondrial outer membrane permeabilization (MOMP), the release of cytochrome c, and caspase activation, ultimately resulting in programmed cancer cell death (apoptosis). In nonclinical studies, venetoclax has demonstrated cytotoxic activity towards a variety of tumour cells derived from B-cell and other hematologic malignancies.

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.

Pharmacokinetics

The pharmacokinetic parameters of venetoclax at steady-state are shown in **Table 9**.

Table 9. Summary of Venetoclax (400 mg) Pharmacokinetic Parameters in Patients with Hematological Malignancies

	Cmax (mcg/mL)	t½ (h)[1]	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. Venetoclax steady state AUC increased proportionally over the dose range of 150 to 800 mg.

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 **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 apparent volume of distribution (Vd_{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.

Excretion

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.

Drug Interactions

For clinically relevant drug interactions, see **DRUG INTERACTIONS**, **Drug-Drug Interactions** above.

Gastric Acid Reducing Agents

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

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.

Special Populations and Conditions

Pediatrics

Pharmacokinetics of VENCLEXTA has not been evaluated in patients less than18 years of age.

Geriatrics

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

Gender

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

Race

Based on population pharmacokinetic analyses with a > 90% Caucasian patient population, race does not have an effect on the pharmacokinetics of venetoclax.

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic 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 two-fold longer in subjects with severe hepatic impairment (median $t_{1/2}$ of 46h; range 15-75h) compared to subjects with normal hepatic function (median $t_{1/2}$ of 17h; range 13-33h) (see **WARNINGS AND PRECAUTIONS**).

Renal Impairment

Based on a population pharmacokinetic analysis that included 211 patients with mild renal impairment (CrCl ≥ 60 and < 90 mL/min, calculated by Cockcroft-Gault equation), 83 subjects with moderate renal impairment (CrCl ≥ 30 and < 60 mL/min) and 210 subjects with normal renal function (CrCl ≥ 90 mL/min), venetoclax exposures in patients with mild or moderate renal

impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl < 30 mL/min) or subjects on dialysis (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY

Store between 2 and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VENCLEXTA (venetoclax) is available as 10 mg, 50 mg, and 100 mg film-coated tablets.

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

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

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

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 wallet blister pack containing 14 tablets of 10 mg
- A wallet blister pack containing 7 tablets of 50 mg
- 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

Listing of Non-Medicinal Ingredients

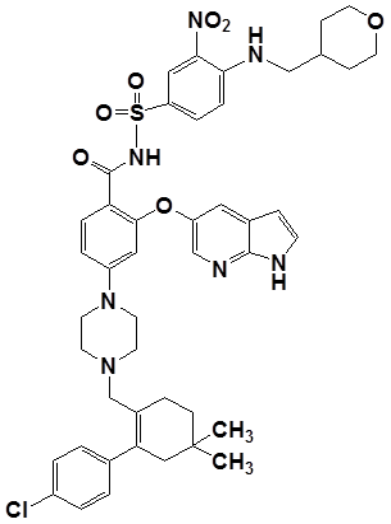
Each 10 mg tablet contains 10 mg of venetoclax with the following non-medicinal ingredients: calcium phosphate dibasic, colloidal silicon dioxide, copovidone, iron oxide yellow, polyethylene glycol, polysorbate 80, polyvinyl alcohol, sodium stearyl fumarate, talc and titanium dioxide.

Each 50 mg tablet contains 50 mg of venetoclax with the following non-medicinal ingredients: 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.

Each 100 mg tablet contains 100 mg of venetoclax with the following 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 dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

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-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide)
Molecular formula and molecular mass:	$C_{45}H_{50}ClN_7O_7S$ and 868.44 g/mol
Structural formula:	
Physicochemical properties:	Venetoclax is a light yellow to dark yellow solid and has very low aqueous solubility.

CLINICAL TRIALS

VENCLEXTA in Combination with Rituximab

MURANO was a randomized (1:1), multicenter, open-label Phase 3 study 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 venetoclax were excluded.

Patients in the VENCLEXTA + rituximab arm completed the 5-week ramp-up schedule of VENCLEXTA (see **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/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2 to 6. Each cycle was 28 days. Patients randomized to bendamustine + rituximab received bendamustine at 70 mg/m^2 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 10**).

Table 10. 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 ≥ 25 x 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
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 progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Treatment with VENCLEXTA + rituximab demonstrated a statistically significant 81% reduction in the risk of progression or death (hazard ratio: 0.19 [95% CI: 0.13, 0.28]; P<0.0001, **Table 11** and **Figure 1**).

The key secondary endpoints were IRC-assessed complete response (CR/CRi) rate, best overall response rate (ORR) and overall survival. The CR/CRi rate was 8% in the VENCLEXTA + rituximab arm and 4% in the bendamustine + rituximab arm (**Table 11**). 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 11**). At the time of the 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 11. Efficacy Results for MURANO by IRC Assessment (ITT Population)

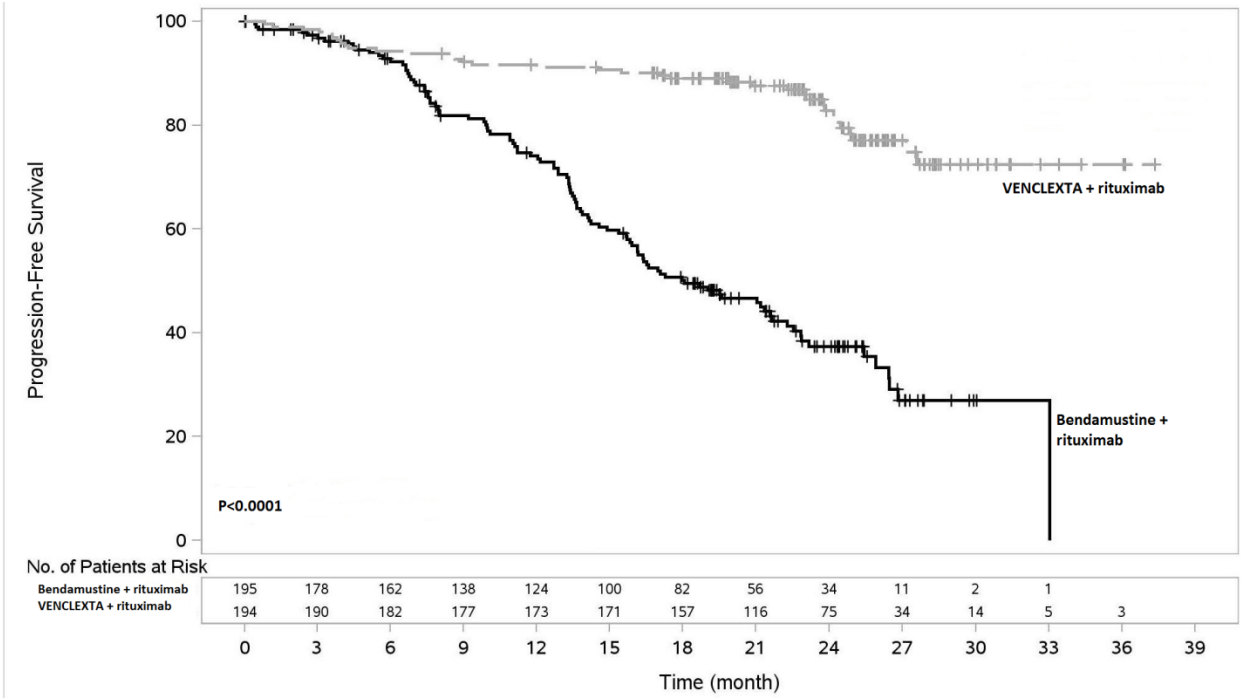
	VENCLEXTA + Rituximab (N = 194)	**Bendamustine + Rituximab (N = 195)**
Progression-free survival		
Number of events (%)	35 (18.0)	106 (54.4)
Disease progression	26 (13)	91 (47)
Death events	9 (5)	15 (8)
Median, months, (95% CI)	Not reached	18.1 (15.8, 22.3)
HR (95% CI)[a]	0.19 (0.13, 0.28)	
p-value	p < 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

	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)

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

[a] 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.

Figure 1. 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 cutoff 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).

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 12** summarizes the baseline demographic and disease characteristics of the study population.

Table 12. 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 (%)	
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 ≥ 25 x 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 *IGHV* 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 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in **Table 13**.

Table 13. Efficacy Results in Study M13-982

Endpoint	IRC Assessment N = 107[a]
ORR, n (%)	85 (79.4)
(95% CI)	(70.5, 86.6)
CR + CRi, n (%)	8 (7.5)
nPR, n (%)	3 (2.8)
PR, n (%)	74 (69.2)

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.

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 cutoff 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.

Minimal residual disease (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 cutoff for a negative status was one CLL cell per 10^4 leukocytes in the sample (i.e., an MRD value of $< 10^{-4}$ was considered MRD negative). 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 ≥ 25 x 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 14**.

Table 14. Efficacy Results in Study M14-032

	IRC Assessment		
Endpoint	**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)

Endpoint	IRC Assessment		
	Ibrutinib Failures N = 91	Idelalisib Failures N = 36	All Patients N = 127

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 22.1months (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 ≥ 25×10^9/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%).

DETAILED PHARMACOLOGY

Pharmacodynamics

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 EC_{50} 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 (EC_{50}: 8 nM) or BCL-X_L-dependent H146 cells (EC_{50}: 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.

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).

Pharmacokinetics

For details regarding the venetoclax pharmacokinetics, refer to **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**.

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 ≥ 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.

Mutagenicity and Carcinogenicity

Carcinogenicity studies have not been conducted with venetoclax.

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

Reproductive and Developmental Toxicity

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/m^2 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 [^{14}C]-venetoclax-derived radioactivity selectively associates with tissues containing melanin.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrVENCLEXTA®

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.

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 weekly over 5 weeks up to the full dose.
  - Your doctor will do blood tests during the first 5 weeks 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. 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?

VENCLEXTA is used to treat patients with chronic lymphocytic leukemia (CLL) when the disease has come back or has not responded to treatment.

CLL is a type of cancer that affect 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.

VENCLEXTA may be given to you alone or in combination with another medicine called rituximab.

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 any of the ingredients.
- You are taking certain medicines when you start your treatment and during the time when your dose is gradually being increased (usually over 5 weeks) because they may have a strong interaction with VENCLEXTA. Some of these medicines include:
    - itraconazole, ketoconazole, posaconazole or voriconazole for fungal infections
    - clarithromycin for bacterial infections
    - ritonavir 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 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:

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 5 weeks of treatment. 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.

- 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. 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.

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 rituximab.

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, contraception 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 (contraception) 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 list contains examples of food or drugs that 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 immunosupressant 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.

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 five weeks of VENCLEXTA.
        - You will receive VENCLEXTA for two years.

- 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.

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.

Side effects may include:

- diarrhea or constipation
- nausea
- vomiting
- stomach pain
- swelling of your arms, legs, hands and feet
- mouth sores
- shortness of breath
- rash
- fever
- headache
- dizziness

- feeling tired
- cough
- muscle and joint pain
- itching

VENCLEXTA may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them		
Symptom/effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
VERY COMMON		
Neutropenia (low levels of white blood cells): chills, fever, sweating or any signs of infection	✓	
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	✓	
COMMON		
Pneumonia (infection of the lungs): chills, cough with or without mucus, fever, shortness of breath	✓	
Respiratory tract infection: runny nose, sore throat or cough	✓	
Urinary tract infection: burning sensation during urination, low urine output despite feeling urge to urinate more often	✓	

Serious side effects and what to do about them		
Symptom/effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
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		✓
Sepsis (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		✓
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 (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting) 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 most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.canada.ca/en/health-canada), the manufacturer's website (abbvie.ca), or by calling 1-888-704-8271.

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