

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**Pr VENCLEXTA<sup>®</sup>**  
venetoclax tablets  
10 mg, 50 mg and 100 mg

Other Antineoplastic Agent

*VENCLEXTA, indicated as monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without the 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VENCLEXTA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>*

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**This product has been authorized under the  
Notice of Compliance with Conditions (NOC/c)**

**What is a Notice of Compliance with Conditions (NOC/c)?**

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

**What will be different about this Product Monograph?**

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

**Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph**

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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# VENCLEXTA

venetoclax tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

*VENCLEXTA, indicated as monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without the 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VENCLEXTA please refer to Health Canada's Notice of Compliance with conditions - drug products web site:*

<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>

## SUMMARY PRODUCT INFORMATION

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

## NOC/c INDICATIONS AND CLINICAL USE

VENCLEXTA (venetoclax) is indicated as monotherapy for the treatment of patients with chronic lymphocytic leukemia (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 interim analyses of single-arm studies. Clinical trial data in patients who do not harbour the 17p deletion are limited (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):**

Of the 164 patients with previously treated CLL evaluated for efficacy 56% were ≥ 65 years of age and 17% were ≥ 75 years of age. No overall difference in effectiveness was observed between these and younger patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Of the 240 patients with CLL evaluated for safety from 3 open-label studies, 58% were ≥ 65 years of age and 17% were ≥ 75 years of age. No overall difference in safety was observed between these patients and younger patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

**NOC/c 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**).

## NOC/c 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 is a significant adverse drug reaction 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.

### **Carcinogenesis and Mutagenesis**

In the pooled VENCLEXTA 400 mg monotherapy safety database, other malignancies, most frequently skin cancers, occurred in 12% of patients treated with VENETOCLAX. Non-melanoma skin cancers occurred in 8% of patients, and non-skin related malignancies occurred in 4% of patients. Causality with VENCLEXTA has not been determined. Monitor patients for the appearance of non-melanoma skin cancers. No carcinogenicity studies 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 4**) 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 was reported in 45% of patients treated with 400 mg VENCLEXTA in clinical trials, with Grade 3 or 4 neutropenia reported in 41% 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**

In the pooled VENCLEXTA 400 mg monotherapy safety database, infections were reported in 65% of patients, with Grade  $\geq 3$  events for 18%. The most common infections were upper respiratory tract infection (22%), nasopharyngitis (9.2%), pneumonia (7.5%), and urinary tract infection (6.3%). The most common serious adverse events of infection were pneumonia (5%) and upper respiratory tract infection (1%). Causality with VENCLEXTA cannot be ruled out.

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

### **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 ( $\text{CrCl} \geq 30$  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 ( $\text{CrCl} < 30$  mL/min) or patients on dialysis.

In clinical trials, the incidence of TLS was higher for subjects with moderate renal impairment (6%) compared to those with normal renal function (4.4%). Patients with reduced renal function ( $\text{CrCl} < 80$  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)**

No overall differences in safety or effectiveness were observed between older and younger patients.

No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

### **Hepatic Impairment**

No specific clinical trials have been completed in subjects with 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**). However, a trend for increased adverse events was observed in patients with moderate hepatic impairment; and hence these patients should be monitored more closely for signs of toxicity at initiation and during the dose ramp-up phase (see **ADVERSE REACTIONS**).

Safety in patients with severe hepatic impairment has not been established. It is not recommended to administer VENCLEXTA to patients with severe hepatic impairment.

## **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.

## **NOC/c ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The safety of VENCLEXTA (venetoclax) has been assessed in a pooled safety database of 240 patients with previously treated CLL who were treated with VENCLEXTA in two Phase 2 trials and one Phase 1 trial. The trials enrolled patients with previously treated CLL, including 160 patients with 17p deletion. Patients were treated with venetoclax 400 mg monotherapy once daily following a dose ramp-up schedule.

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

Serious adverse reactions were reported in 44% of patients. The most frequently reported serious adverse reactions ( $\geq 2\%$ ) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia, anemia, and TLS.

Discontinuations due to adverse reactions occurred in 8.3% of patients. The most frequent adverse reactions leading to VENCLEXTA discontinuation were autoimmune hemolytic anemia and thrombocytopenia.

Dosage adjustments due to adverse reactions occurred in 9.6% of patients. The adverse reactions most frequently leading to dose reduction were neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, vomiting, and pneumonia.

## **Tumour Lysis Syndrome**

Tumour lysis syndrome is an important identified risk when initiating VENCLEXTA. 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 66 patients with CLL (64 previously treated, 2 previously untreated) starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. 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 3**).

## **Clinical Trial Adverse Events**

*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.*

Adverse events described in **Table 1** below reflect exposure to single agent VENCLEXTA in a single-arm Phase 2 clinical study (M13-982) of 107 patients with previously treated CLL harbouring the 17p deletion. The median duration of treatment was 12.1 months.

**Table 1. Adverse Events Reported in  $\geq 10\%$  (Any Grade) or  $\geq 5\%$  (Grade 3 or 4) of Patients with Previously Treated CLL Harboring the 17p Deletion<sup>a</sup> (Study M13-982)**

System Organ Class Adverse event <sup>b</sup>	VENCLEXTA (N = 107)	
	Any Grade (%)	Grade 3 or 4 (%)
<b>Blood and lymphatic system disorders</b>		
Neutropenia	43	40
Anemia	27	18
Thrombocytopenia	19	15
Autoimmune hemolytic anemia	7	7
<b>Gastrointestinal disorders</b>		
Diarrhea	29	0
Nausea	29	1
Vomiting	15	1
Constipation	10	0
<b>General disorders and administration site conditions</b>		

	<b>VENCLEXTA (N = 107)</b>	
<b>System Organ Class</b> Adverse event <sup>b</sup>	<b>Any Grade (%)</b>	<b>Grade 3 or 4 (%)</b>
Fatigue	21	0
Pyrexia	20	1
<b>Infections and infestations</b>		
Upper respiratory tract infection	15	2
Nasopharyngitis	14	0
Pneumonia	8	5
<b>Metabolic and nutrition disorders</b>		
Hyperphosphatemia	16	1
Hypokalemia	10	3
<b>Musculoskeletal and connective tissue disorders</b>		
Back pain	10	2
<b>Nervous system disorders</b>		
Headache	11	0

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

b. Adverse event of malignant neoplasm progression is not included as it is considered disease progression.

Adverse events described in **Table 2** below reflect exposure to single agent VENCLEXTA in a single-arm Phase 1 dose escalation study (M12-175) of patients with previously treated CLL, in which 57 patients (45 of whom did not have the 17p deletion) were treated with VENCLEXTA 400 mg for a median duration of 11.5 months.

**Table 2. Adverse Events Reported in  $\geq 10\%$  (Any Grade) or  $\geq 5\%$  (Grade 3 or 4) of Patients with Previously Treated CLL (Study M12-175)**

	<b>VENCLEXTA (N = 57)</b>	
<b>System Organ Class</b> Adverse Event	<b>Any Grade (%)</b>	<b>Grade 3 or 4 (%)</b>
<b>Blood and lymphatic system disorders</b>		
Neutropenia	44	40
Anemia	37	19
Thrombocytopenia	23	12
<b>Gastrointestinal disorders</b>		
Diarrhea	47	0
Nausea	40	2

	<b>VENCLEXTA</b> (N = 57)	
<b>System Organ Class</b>	<b>Any Grade (%)</b>	<b>Grade 3 or 4 (%)</b>
Adverse Event		
Constipation	19	0
Vomiting	18	2
Abdominal pain	14	2
<b>General disorders and administration site conditions</b>		
Fatigue	32	5
Pyrexia	18	0
Peripheral edema	16	0
<b>Infections and infestations</b>		
Upper respiratory tract infection	40	2
Sinusitis	11	0
Pneumonia	7	5
<b>Investigations</b>		
Aspartate aminotransferase increased	14	2
Neutrophil count decreased	14	12
Blood lactate dehydrogenase increased	5	5
<b>Metabolic and nutrition disorders</b>		
Hyperglycemia	16	7
Hyperphosphatemia	16	0
Hypokalemia	16	7
Hypocalcemia	16	4
Hypophosphatemia	7	5
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	19	2
Back pain	11	0
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>		
Squamous cell carcinoma of skin	14	9
Basal cell carcinoma	7	5
<b>Nervous system disorders</b>		
Headache	28	2
Dizziness	14	0
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	26	0
Nasal congestion	11	0

	VENCLEXTA (N = 57)	
System Organ Class Adverse Event	Any Grade (%)	Grade 3 or 4 (%)
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	14	0

### **Abnormal Hematologic and Clinical Chemistry Findings**

Treatment-emergent laboratory abnormalities relevant to TLS observed in 66 patients with CLL who followed the dose ramp-up schedule and TLS prophylaxis measures are presented in **Table 3**.

**Table 3. Treatment-Emergent Adverse Events: TLS and Relevant Laboratory Abnormalities Reported in Patients with CLL**

	VENCLEXTA (N = 66)	
Laboratory Parameter	Any Grade (%)	Grade 3 (%)
Laboratory TLS <sup>a</sup>	6	6
Hyperkalemia <sup>b</sup>	20	2
Hyperphosphatemia <sup>c</sup>	15	3
Hypocalcemia <sup>d</sup>	9	3
Hyperuricemia <sup>e</sup>	6	2

a. Laboratory abnormalities that met  $\geq 2$  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.

## **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  $AUC_{\infty}$  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  $AUC_{\infty}$  by 78%.

Avoid concomitant use of P-gp inhibitors (e.g., amiodarone, azithromycin, 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 and ramp-up doses of VENCLEXTA by at least 50%. Monitor patients more closely for VENCLEXTA toxicities.

For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by 50% when used concomitantly with P-gp inhibitors. Resume the VENCLEXTA dose that was used prior to initiating the P-gp inhibitor 1 day after discontinuation of the inhibitor (see **DOSAGE AND ADMINISTRATION**).

### CYP3A Inducers

Co-administration of once daily rifampin, a strong CYP3A inducer, decreased venetoclax  $C_{max}$  by 42% and  $AUC_{\infty}$  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  $AUC_{\infty}$ .

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  $AUC_{\infty}$  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**

VENCLEXTA (venetoclax) should be taken orally once daily until disease progression or unacceptable toxicity is observed. Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed or broken prior to swallowing.

### **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 ( $\text{CrCl} < 80 \text{ ml/min}$ ) 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 4**).

**Table 4** below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

**Table 4. 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 <sup>c,d</sup>
		Hydration <sup>a</sup>	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN < 5 cm AND ALC < 25 x10 <sup>9</sup> /L	Oral (1.5 to 2 L)	Allopurinol <sup>b</sup>	Outpatient <ul style="list-style-type: none"> <li>Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg</li> <li>Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion</li> </ul>
Medium	Any LN 5 cm to < 10 cm OR ALC ≥25 x10 <sup>9</sup> /L	Oral (1.5 to 2 L) and consider additional intravenous	Allopurinol	Outpatient <ul style="list-style-type: none"> <li>Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg</li> <li>Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion</li> <li>Consider hospitalization for patients with CrCl &lt; 80ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital</li> </ul>
High	Any LN ≥ 10 cm OR ALC ≥ 25 x10 <sup>9</sup> /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 <ul style="list-style-type: none"> <li>Pre-dose, 4, 8,12 and 24 hours</li> </ul> Outpatient at subsequent ramp-up doses <ul style="list-style-type: none"> <li>Pre-dose, 6 to 8 hours, 24 hours</li> </ul>

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**

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 recommended daily dose of 400 mg over a period of 5 weeks as shown in **Table 5**. The 5-week ramp-up dosing schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of TLS. The recommended steady daily dose is 400 mg thereafter.

**Table 5. Dosing Schedule for Ramp-Up Phase**

<b>Week</b>	<b>VENCLEXTA Daily Dose</b>
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 and beyond	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**).

### **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 when at the daily dose of 400 mg, 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).

#### **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 6**). 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 6** 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 6. Dose Reduction for Toxicity During VENCLEXTA Treatment**

Dose at Interruption, mg	Restart Dose, mg <sup>a</sup>
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 (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). A recommended dose has not been determined for patients with severe hepatic impairment.

No dose adjustment is recommended for patients with mild or moderate renal impairment ( $\text{CrCl} \geq 30$  mL/min). A recommended dose has not been determined for patients with severe renal impairment ( $\text{CrCl} < 30$  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 and ramp-up doses of VENCLEXTA by at least 50%. Monitor patients more closely for signs of toxicities.

For patients who have completed the ramp-up phase and are on steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by 50% when used concomitantly with P-gp inhibitors. Monitor patients more closely for 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.

## **NOC/c 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 7**.

**Table 7. Summary of Venetoclax (400 mg) Pharmacokinetic Parameters in Patients with Hematological Malignancies**

	<b>C<sub>max</sub> (mcg/mL)</b>	<b>t<sub>1/2</sub> (h)<sup>1</sup></b>	<b>AUC<sub>0-24</sub> (mcg*h/mL)</b>	<b>CL/F (L/h)</b>	<b>V<sub>dss</sub>/F<sup>1</sup> (L)</b>
<b>Steady-state mean (%CV)</b>	2.10 (53)	26 (17)	32.8 (52)	16.5 (66)	256–321 (32)

<sup>1</sup>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 (V<sub>dss</sub>/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 of venetoclax was approximately 26 hours. After a single oral administration of 200 mg radiolabeled [<sup>14</sup>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 than 18 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, 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. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

### **Renal Impairment**

Based on a population pharmacokinetic analysis that included 211 patients with mild renal impairment ( $\text{CrCl} \geq 60$  and  $< 90$  mL/min, calculated by Cockcroft-Gault equation), 83 subjects with moderate renal impairment ( $\text{CrCl} \geq 30$  and  $< 60$  mL/min) and 210 subjects with normal renal function ( $\text{CrCl} \geq 90$  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 ( $\text{CrCl} < 30$  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 7days)
- A Week 3 wallet blister pack containing a blister card of 7 tablets (i.e., one 100 mg tablet per day for 7days)
- A Week 4 wallet blister pack containing a blister card of 14 tablets (i.e., two 100 mg tablets per day for 7days)

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

*VENCLEXTA (venetoclax), indicated as monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without the 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VENCLEXTA please refer to Health Canada's Notice of Compliance with conditions - drug products web site:*

<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>

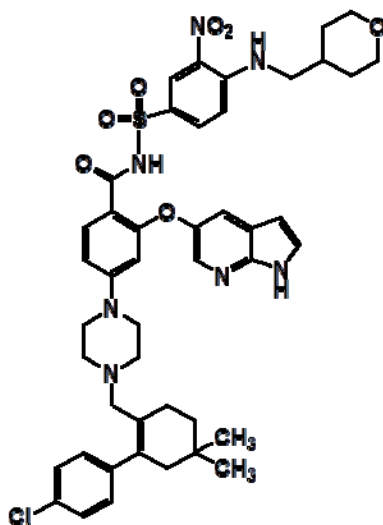
### PHARMACEUTICAL INFORMATION

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-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide)

Molecular formula and molecular mass: C<sub>45</sub>H<sub>50</sub>ClN<sub>7</sub>O<sub>7</sub>S and 868.44 g/mol

Structural formula:



Physicochemical properties:

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

## NOC/c CLINICAL TRIALS

The safety and efficacy of VENCLEXTA (venetoclax) in patients with CLL who have received at least one prior therapy were evaluated in one single-arm Phase 2 clinical trial (M13-982), and one single-arm Phase 1 trial (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 8** summarizes the baseline demographic and disease characteristics of the study population.

**Table 8. Demographic and Baseline Characteristics of Patients in Study M13-982**

Characteristics	M13-982 N = 107 <sup>a</sup>
<b>Age (years)</b> Median (range)	67 (37–85)
<b>Gender, n (%)</b> Male Female	70 (65.4) 37 (34.6)
<b>Race, n (%)</b> White Other	103 (97.2) 4 (2.1)
<b>Eastern Cooperative Oncology Group (ECOG) performance status</b> 0 1 2	39.3 52.3 8.4
<b>Tumour burden, %</b> Absolute lymphocyte count $\geq 25 \times 10^9/L$ One or more nodes > 5 cm	50.5 53.3
<b>Number of prior therapies; median (range)</b>	2 (1–10)
<b>Time since diagnosis, months; median (range)</b>	81.7 (1.2–385.6) <sup>b</sup>

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 venetoclax 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 venetoclax 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 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results are shown in **Table 9**.

**Table 9. Efficacy Results in Study M13-982**

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

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. Median DOR has not been reached with approximately 12 months median follow-up.

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 venetoclax treatment. The cutoff for a negative status was one CLL cell per 10<sup>4</sup> leukocytes in the sample (i.e., an MRD value of < 10<sup>-4</sup> was considered MRD negative). Seventeen percent (18/107) of patients were MRD negative in the peripheral blood, including 6 patients who were also MRD negative in the bone marrow.

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 M12-175**

Study M12-175 was a Phase 1, multi-center, open-label trial of patients with previously treated CLL who had relapsed following or were refractory to standard treatments, and for whom no other therapies were available. The study included 45 patients with CLL without 17p deletion 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 11.5 months (range: 0.5 to 34.1 months).

An overall response rate of 75.6% was reported for the 45 patients with relapsed or refractory CLL without the 17p deletion, as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008).

## **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<sub>50</sub> 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<sub>max,ss</sub> 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<sub>max</sub> = 16 mcg/mL; 7.6 times the human C<sub>max,ss</sub> 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<sub>max</sub> = 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  $\geq 30$  mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversibly decreases in lymphocytes at  $\geq 10$  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<sup>2</sup> 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 [<sup>14</sup>C]-venetoclax-derived radioactivity selectively associates with tissues containing melanin.

## **REFERENCES**

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

VENCLEXTA<sup>®</sup> (venetoclax) is used in the treatment of patients with chronic lymphocytic leukemia (CLL) who were previously treated for their cancer.

It has been approved *with conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

**PrVENCLEXTA<sup>®</sup>**

**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 a serious side effect known as 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.

### **What is VENCLEXTA used for?**

VENCLEXTA is used to treat patients with chronic lymphocytic leukemia (CLL) who were previously treated for their cancer.

### **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:**

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.

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

**How to take VENCLEXTA:**

- Always take VENCLEXTA exactly as your doctor tells you.
- Drink plenty of water when taking VENCLEXTA to help reduce your risk of getting TLS.
- Take the tablets with a meal and water at the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break the tablets.

**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. You will stay on the 400 mg daily dose, which is the standard dose, for as long as necessary.

**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
- headache
- feeling tired

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



<b>Serious side effects and what to do about them</b>		
Symptom/effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
<b>VERY COMMON</b>		
<b>Neutropenia</b> (low levels of white blood cells): chills, fever, sweating or any signs of infection	✓	
<b>Anemia</b> (low levels of red blood cells): fatigue, pale skin, shortness of breath, weakness	✓	
<b>Thrombocytopenia</b> (low levels of blood platelets): increases risk of bleeding or bruising	✓	
<b>COMMON</b>		
<b>Pneumonia</b> (infection of the lungs): chills, cough with or without mucus, fever, shortness of breath	✓	
<b>Upper respiratory tract infection:</b> runny nose, sore throat or cough	✓	
<b>RARE</b>		
<b>Tumour lysis syndrome (TLS):</b> chills, confusion, dark or cloudy urine, fever, irregular heartbeat, joint discomfort, muscle pain, nausea, shortness of breath, seizure, tiredness, vomiting		✓

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](http://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](http://www.canada.ca/en/health-canada) ([www.canada.ca/en/health-canada](http://www.canada.ca/en/health-canada)), the manufacturer's website ([abbvie.ca](http://abbvie.ca)), or by calling 1-888-704-8271.

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