Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

venetoclax

COMMON TRADE NAME(S): Venclexta®

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B - Mechanism of Action and Pharmacokinetics

Venetoclax is an oral selective small-molecule B-cell lymphoma (BCL)-2 inhibitor (a protein that inhibits apoptosis). BCL-2 overexpression has been associated with resistance to chemotherapies by binding and sequestering high levels of BH3 motif-containing pro-apoptotic proteins. Venetoclax binds to the BH3-binding groove of BCL-2, displacing pro-apoptotic proteins to initiate mitochondrial outer membrane permeabilization (MOMP), the release of cytochrome c, and caspase activation, ultimately resulting in apoptosis.

Absorption	Peak plasma levels	Reached 5 to 8 hours after dose
	Effects with food	Low-fat meal ↑ exposure by approx. 3.4 fold High-fat meal ↑ exposure by 5.1 to 5.3 fold
Distribution	PPB	Highly bound to human plasma protein
Metabolism	Main enzymes involved	CYP3A
	Active metabolites	Yes
Elimination	Half-life	26 hours
	Feces	> 99.9%

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Urine	< 0.1%

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C - Indications and Status

Health Canada Approvals:

- Chronic lymphocytic leukemia (CLL)
- Acute myeloid leukemia (AML)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Small lymphocytic lymphoma

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following adverse effects were reported in ≥ 10% (all grades) or ≥ 5% (≥ Grade 3) of patients with previously treated CLL in pooled data from phase I or II single-arm trials. Severe or life-threatening adverse effects are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Rash, pruritus (19%)	E D
Gastrointestinal	Abdominal pain (20%) (3% severe)	E
	Constipation (17%)	E
	Diarrhea (46%) (3% severe)	E
	Mucositis (14%)	E
	Nausea, vomiting (43%)	E
General	Edema (22%) (2% severe)	E D
	Fatigue (34%) (4% severe)	E D

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	Other (rare) (multiple organ dysfunction syndrome)	E D
Hematological	Hemolytic anemia (<10%)	E
	Myelosuppression ± infection, bleeding (52%) (46% severe)	E D
Metabolic / Endocrine	Abnormal electrolyte(s) (18%) (↑ PO4, ↓/↑ K, ↓ Ca, ↓ Mg; 5% severe)	E D
	Hyperuricemia (7%) (3% tumour lysis syndrome)	E
Musculoskeletal	Musculoskeletal pain (31%) (2% severe)	E
Neoplastic	Secondary malignancy (19%) (including non-melanoma skin 9%, non-skin 9%)	D L
Nervous System	Dizziness (15%)	E
	Headache (19%)	E
Respiratory	Cough, dyspnea (24%) (1% severe)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for venetoclax include myelosuppression ± infection, bleeding, diarrhea, nausea, vomiting, fatigue, musculoskeletal pain, cough, dyspnea, edema, abdominal pain, headache, rash and pruritus.

Other malignancies occurred in 19% of patients in a pooled monotherapy safety database. They were also reported in combination with rituximab.

Tumour lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, was reported in patients with high tumour burden, but the incidence is reduced when the dose is ramped up. Changes in blood chemistries that require prompt management can occur as early as 6-8 hours after the first dose and at each dose increase. Patients should not take their next dose until 24-hour blood chemistry results have been assessed. TLS may also occur when resuming venetoclax after a dose interruption. Reduced renal function (CrCl ≤ 80mL/min) and splenomegaly increase the risk. All patients should be assessed for risk and receive TLS prophylaxis with hydration and anti-hyperuricemics prior to starting treatment; more intensive management, including hospitalization, may be required if high risk.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Correct potassium, uric acid, phosphorus, calcium, and creatinine abnormalities prior to initiation.

Consider supportive measures such as antimicrobials for signs of infection, and prophylactic use of G-CSF according to local guidelines.

Prophylaxis for TLS (in CLL patients)

- **Tumour lysis prophylaxis** (i.e. adequate hydration and anti-hyperuricemic agents) prior to and during ramp-up phase **is required for all patients**.
- Prophylaxis based on tumour burden in table below.

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 x 10^9/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 x 10^9/L	Oral (1.5 to 2 L) and consider additional IV	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

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				doses, and post-dose at clinical discretion • Consider hospitalization if CrCl < 80 mL/min at first dose of 20 mg and 50 mg; see below
High	Any LN ≥ 10 cm OR ALC ≥ 25 x 10^9/L AND any LN ≥ 5 cm	Oral (1.5 to 2 L) and IV (150 to 200 mL/hr, as tolerated)	Allopurinol; consider rasburicase if elevated uric acid at baseline	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. Start oral hydration 2 days before and continue during ramp-up. Administer IV hydration if unable to tolerate oral.
b. Start allopurinol or xanthine oxidase inhibitor for 2-3 days prior to starting venetoclax.
c. Evaluate blood chemistries (potassium, phosphorus, uric acid, calcium, creatinine); review in real time.
d. For patients at continued risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

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Prophylaxis for TLS (in AML patients)

- **Tumour lysis prophylaxis** (i.e. adequate hydration and anti-hyperuricemic agents) prior to and during ramp-up phase **is required for all patients.**
- All patients should have white blood cell count less than 25×10^9 /L prior to initiation.
- Monitor blood chemistry pre-dose and 6 to 8 hours after each dose increase, and 24 hours after final dose.
- For patients at high risk for TLS (e.g., circulating blasts, high burden, elevated LDH levels, or reduced renal function), consider increased laboratory monitoring or dose reduction.
- Consider hospitalization on or before initiation and until 24 hours after reaching maximum dose, according to local practices.

Adults:

For CLL:

- Concomitant use with **strong CYP3A inhibitors** is **contraindicated during initiation and ramp-up phase**.
- Refer to Interactions section for dosing recommendations when co-administered with **CYP3A or P-gp inhibitors** during **both ramp-up and daily dosing**.
- Refer to regimen monograph(s) for details on dosing schedule.

The venetoclax dose must be administered according to a **5-week ramp-up** schedule to the recommended daily dose.

Table 1: Ramp-up Dosing Schedule for CLL

Week	Venetoclax Dose (mg/day)
1	20
2	50
3	100
4	200
5	400

Daily Dose for CLL (After Ramp-up Phase): 400 mg po daily

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For AML:

- Refer to Interactions section for dosing recommendations when co-administered with **CYP3A or P-gp inhibitors** during **both ramp-up and daily dosing**.
- Refer regimen monograph(s) for details on dosing schedule.

The venetoclax dose must be administered according to a **3- to 4-day ramp-up** schedule to the recommended daily dose.

Table 2: Ramp-up Dosing Schedule for AML

Day	Venetoclax Dose (mg/day)	
	In combination with azacitidine	In combination with low-dose cytarabine
1	100	100
2	200	200
3	400	400
4		600

Daily Dose For AML (After Ramp-up Phase)

Combination with azacitidine: 400 mg po daily

Combination with low-dose cytarabine: 600 mg po daily

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Dosage with Toxicity:

For CLL:

For dose interruptions that last:

- > 1 week during first 5 weeks of ramp-up, or
- > 2 weeks after completing ramp-up,

Reassess for risk of TLS to determine if dose reduction is necessary.

Dose at Interruption (mg/day)	Restart Dose (mg/day)[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 during ramp-up.

Table 3: Dose Modification in CLL

Toxicity/Event	Action*
Blood chemistry suggests TLS	Hold next day's dose. If resolved within 24-48 hours; resume at same dose.
Clinical TLS or blood chemistry changes for ≥ 48 hours	Hold until resolved; resume at a reduced dose (see table above) and follow TLS prophylaxis.
Any Grade 3 or 4 non-hematological	<u>1st occurrence:</u> Hold until ≤ Grade 1 or baseline; resume at same dose. <u>2nd and subsequent occurrence(s):</u> Hold until ≤ Grade 1 or baseline; resume at a reduced dose (see table above). A larger dose reduction may be selected at the discretion of the physician.
≥ Grade 3 neutropenia** with infection or fever	
Grade 4 hematological toxicities (except lymphopenia)	
*For dose reductions to < 100 mg for > 2 weeks, consider discontinuing. **G-CSF may be administered with venetoclax if clinically indicated.	

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For AML:

Table 4: Dose Modification in AML

Toxicity/Event	Timing	Action
Grade 4 neutropenia with or without fever or infection OR Grade 4 thrombocytopenia	Prior to remission	Continue at same dose; monitor blood count.
	After remission;1st occurrence, lasting ≥ 7days:	Hold until < Grade 2; resume at same dose.
	After remission; subsequent occurrence, lasting ≥ 7 days:	Hold until < Grade 2; resume at the same dose but reduce venetoclax duration by 7 days for subsequent cycles (e.g. 21 days of treatment instead of 28 days).
Any Grade 3 or 4 non-hematological	Any	Hold until ≤ Grade1 or baseline; resume at same dose.
Clinically significant laboratory or clinical TLS	Any	Hold until resolved. Manage promptly.

Dosage with Hepatic Impairment:

Monitor closely for toxicity at initiation and during ramp-up phase.

Bilirubin		AST	Venetoclax Dose
≤ ULN	and	> ULN	No dose adjustment
>1 - 3 x ULN	and	Any	
>3 x ULN	and	Any	50% reduction

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Dosage with Renal Impairment:

Patients with reduced renal function (CrCl < 80 mL/min) have an increased risk of TLS and may require more intensive TLS prophylaxis and monitoring.

Creatinine Clearance (mL/min)	Venetoclax Dose
≥ 30	No dose adjustment
< 30	Limited data

Dosage in the elderly:

No dose adjustment required; no overall differences in efficacy or safety observed between patients ≥ 65 years of age and younger patients. Age does not have an effect on pharmacokinetics, based on population PK analyses.

Dosage based on gender:

Gender does not have an effect on clearance, based on population PK analyses.

Dosage based on ethnicity:

Asian patients had 67% higher exposure than non-Asian patients; however, no dose adjustment is necessary.

Children:

No safety and efficacy data available.

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F - Administration Guidelines

Note: Venetoclax is only available through pharmacies that are part of AbbVie's managed distribution program.

- Administer venetoclax with a meal and water at approximately the same time each day.
- Tablets should be swallowed whole and not be chewed, crushed, or broken prior to swallowing.
- If a dose is missed, it should be taken as soon as possible (within 8 hours of the time it is normally taken). If > 8 hours, the dose should be skipped and the usual dosing schedule resumed the following day.
- If the patient vomits after taking a dose, no additional dose should be taken. The next dose should be taken at the usual time.
- Grapefruit products, Seville oranges, and starfruit must not be used during the ramp-up period and should be avoided during treatment.
- Store between 2 and 30°C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.
- Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL.

Other Warnings/Precautions:

- Tumour lysis syndrome (see Dosing section for prophylaxis).
- Safety and efficacy of live attenuated vaccines during or after treatment have not been studied. Live vaccines should not be administered during treatment and thereafter until B-cell recovery. Patients should be advised that vaccinations may be less effective.

Other Drug Properties:

- Carcinogenicity:
  Second primary malignancies have been reported; however, no formal carcinogenic studies have been performed.
- Phototoxicity: No

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Pregnancy and Lactation:

- Fetotoxicity: Likely
  Venetoclax is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **30 days** after the last dose.
- Excretion into breast milk: Unknown
  Do not breastfeed during treatment; it is unknown whether venetoclax or metabolites are excreted in human milk.
- Fertility effects: Likely
  Testicular germ cell depletion was observed in animals; male fertility may be compromised.

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H - Interactions

- Venetoclax is predominantly metabolized by CYP3A4.
- Venetoclax is also a P-gp and BCRP substrate, a P-gp and BCRP inhibitor, and a weak OATP1B1 inhibitor (in vitro).
- No dose adjustment is needed when co-administered with azithromycin.
- Gastric acid agents did not affect bioavailability in population PK analysis.
- In vitro studies at clinically relevant concentrations showed that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A4. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7, and not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

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Table 5: Drug Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, itraconazole, voriconazole, posaconazole)	↑ venetoclax concentration and/or toxicity	↓ metabolism	Refer to **table 6** for dose modifications when co-administered with CYP3A or P-gp Inhibitors. For CLL only: Concomitant use with strong CYP3A inhibitors is **contraindicated during initiation and ramp-up phase.**
Moderate CYP3A inhibitors (i.e. erythromycin, ciprofloxacin, diltiazem, fluconazole, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ venetoclax concentration and/or toxicity	↓ metabolism	Refer to **table 6** for dose modifications when co-administered with CYP3A or P-gp Inhibitors.
P-glycoprotein inhibitors (i.e. quinidine, amiodarone, carvedilol, captopril, felodipine, verapamil, cyclosporine)	↑ venetoclax concentration and/or toxicity	↓ metabolism	Refer to **table 6** for dose modifications when co-administered with CYP3A or P-gp Inhibitors.
CYP3A inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, bosentan, efavirenz, modafinil, etc)	↓ venetoclax concentration and/or efficacy	↑ metabolism	Avoid concomitant use with both strong and moderate inducers; consider alternative treatments.
P-glycoprotein substrates (i.e. digoxin, everolimus, sirolimus) and BCRP substrates	↑ substrate concentration and/or exposure	Venetoclax is a P-gp and BCRP inhibitor *(in vitro)*	Avoid drugs with narrow therapeutic index. If P-gp substrates must be used, administer at least 6 hours before venetoclax.
Warfarin	↑ warfarin concentration and/or toxicity		Caution; monitor INR closely.

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Table 6: Dose Modification when Co-administered with CYP3A or P-gp Inhibitors

Agent	Venetoclax Dose at Initiation and Ramp-up Phase (mg/day)	Venetoclax Daily Dose (After Ramp-up Phase) (mg/day)
Strong CYP3A inhibitor	**CLL: Contraindicated**	Avoid concomitant use. If unavoidable, reduce venetoclax dose to 100 mg or less.
	AML: Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg or less	Reduce venetoclax dose to 100 mg or less.
Moderate CYP3A inhibitor	CLL: Avoid concomitant use. If unavoidable, reduce venetoclax dose by at least 50%.	
	AML: Reduce venetoclax dose by at least 50%.	
P-gp inhibitor	CLL and AML: Reduce venetoclax dose by at least 50%.†	

†Venetoclax dose adjustment is not required when co-administered with azithromycin.

Resume the venetoclax dose that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Tumour burden assessment	Prior to starting treatment
CBC	Baseline, at each visit, and as clinically indicated
Liver function tests	Baseline, at each visit, and as clinically indicated
Blood chemistry and electrolytes (for TLS - including potassium, uric acid, phosphorous, calcium, creatinine)	Before starting, 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, at each visit, and as clinically indicated. Also refer to Prophylaxis for TLS section.
INR	Baseline and at each visit, or as clinically indicated (for patients taking warfarin)
Secondary malignancies (including non-melanoma skin and non-skin)	At each visit
Clinical toxicity assessment for bleeding, infection, GI effects, fatigue, edema, musculoskeletal pain, rash, and headache	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- venetoclax - Treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), based on criteria
- venetoclax - In combination with obinutuzumab for previously untreated chronic lymphocytic leukemia, based on criteria
- venetoclax - Venetoclax in combination with azacitidine - Previously untreated acute myeloid leukemia, based on criteria
- venetoclax - For the treatment of patients with chronic lymphocytic leukemia (CLL), in combination with ibrutinib, based on criteria

High Cost Therapy Funding Program (HCTFP website)

- venetoclax (Inpatient) - Venetoclax in combination with azacitidine - Previously untreated acute myeloid leukemia

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K - References

Agarwal SK et al. Effect of Azithromycin on Venetoclax Pharmacokinetics in Healthy Volunteers: Implications for Dosing Venetoclax with P-gp Inhibitors. Adv Ther. 2018 Nov;35(11):2015-2023.

BC Cancer Drug Manual. Venetoclax. October 2019.

Prescribing Information: Venclexta (venetoclax). Abbvie Inc. 11/2020.

Product Monograph: Venclexta (venetoclax) Product Monograph. AbbVie Corporation. January 2021 and April 2022.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016;17:768-78.

August 2025 Updated Supplementary Public Funding section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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