**Drug Monograph**



## 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<br>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% |

| | |
|---|---|
| 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 |

| | | |
|---|---|---|
| | 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 hospitalisation, 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<br>AND<br>ALC < 25 x $10^9$/L | Oral (1.5 to 2 L) | Allopurinol | Outpatient:<br>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg<br>• Pre-dose at subsequent ramp-up doses, and post-dose at clinical discretion |
| Medium | Any LN 5 cm to < 10 cm<br>OR<br>ALC ≥ 25 x $10^9$/L | Oral (1.5 to 2 L) and consider additional IV | Allopurinol | Outpatient:<br>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg<br>• Pre-dose at subsequent ramp-up |

| | | | | |
|---|---|---|---|---|
| | | | | doses, and post-dose at clinical discretion<br>• Consider hospitalization if CrCl < 80 mL/min at first dose of 20 mg and 50 mg; see below |
| High | Any LN ≥ 10 cm<br><br>OR<br><br>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<br><br>• Pre-dose, 4, 8, 12 and 24 hours<br><br>Outpatient at subsequent ramp-up doses<br><br>• 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.

**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:***

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

Concomitant use with strong CYP3A4 inhibitors is **contraindicated during initiation and ramp-up phase**. Also refer to Section H - Interactions for dosing when co-administered with CYP3A4 or P-gp inhibitors.

**Table 1: Ramp-up Dosing Schedule for CLL**

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

**Steady State Dose for CLL:** 400 mg po daily

*Refer to regimen monograph(s) for details on dosing schedule.*

***For AML:***

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

Also refer to Section H - Interactions for dosing when co-administered with strong and moderate CYP3A4 inhibitors or P-gp inhibitors.

(Continued on next page)

**Table 2: Ramp-up Dosing Schedule for AML**

| Day | Venetoclax Dose (mg/day) | | |
|---|---|---|---|
| | In combination with azacitidine | In combination with low-dose cytarabine | In combination with strong CYP3A4 inhibitors |
| 1 | 100 | 100 | 10 |
| 2 | 200 | 200 | 20 |
| 3 | 400 | 400 | 50 |
| 4 | | 600 | 100 or less |

**Steady State Dose For AML**

*Combination* with azacitidine:* 400 mg po daily

*Combination with low-dose cytarabine:* 600 mg po daily

**Refer regimen monograph(s) for details on dosing schedule.*

***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.<br><br>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><br><br>Hold until ≤ Grade 1 or baseline; resume at same dose.<br><br><u>2nd and subsequent occurrence(s):</u><br><br>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.<br><br>**G-CSF may be administered with venetoclax if clinically indicated. | |

***For AML:***

**Table 4: Dose Modification in AML**

| Toxicity/Event | Timing | Action |
|---|---|---|
| Grade 4 neutropenia with or without fever or infection<br><br>OR<br><br>Grade 4 thrombocytopenia | Prior to remission: | Continue at same dose; monitor blood count. |
| | After remission;1st occurrence, lasting <u>≥</u> 7days: | Hold until < Grade 2; resume at same dose. |
| | After remission; subsequent occurrence, lasting <u>≥</u> 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 |

***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$^{o}$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

### Pregnancy and Lactation:

- Fetotoxicity: Likely
  Venetoclax is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **30 days** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended; 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

- Veneotoclax 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 or expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| Strong CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, itraconazole, voriconazole, posaconazole) | ↑ venetoclax concentration and/or toxicity | ↓ metabolism | *For CLL:*<br><br>**Contraindicated during initiation and ramp-up phase.** At steady state, avoid concomitant use. If concomitant use is required, reduce venetoclax dose to 100 mg or less; resume previous dose 2 to 3 days after stopping the inhibitor.<br><br>*For AML:*<br><br>During initiation and ramp-up phase, see Section E - Dosing (Table 2). At steady state, reduce venetoclax dose to 100 mg or less; resume previous dose 2 to 3 days after stopping the inhibitor. |
| Moderate CYP3A4 inhibitors (i.e. erythromycin, ciprofloxacin, diltiazem, fluconazole, fruit or juice from grapefruit, Seville oranges or starfruit) | ↑ venetoclax concentration and/or toxicity | ↓ metabolism | Avoid concomitant use in CLL.<br><br>Reduce venetoclax dose by at least 50% if concomitant use is unavoidable. Resume previous dose 2 to 3 days after stopping the inhibitor. |
| P-glycoprotein inhibitors (i.e. | ↑ venetoclax concentration and/or | ↓ metabolism | Reduce the venetoclax dose by at least 50%; resume dose 2 to 3 |

| | | | |
|---|---|---|---|
| quinidine, amiodarone, carvedilol, captopril, felodipine, verapamil, cyclosporine) | toxicity | | days after stopping the inhibitor.<br><br>Exception: venetoclax dose adjustment not required when co-administered with azithromycin. |
| CYP3A4 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. verapamil, digoxin, everolimus, sirolimus) and BCRP substrates (i.e. topotecan) | ↑ substrate concentration and/or exposure | Venetoclax is a P-gp and BCRP inhibitior *(in vitro)* | Avoid drugs with narrow therapeutic index; if must be used, administer at least 6 hours before venetoclax. |
| Warfarin | ↑ warfarin concentration and/or toxicity | | Caution; monitor INR closely. |

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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) according to clinical criteria
- venetoclax - In combination with obinutuzumab for previously untreated chronic lymphocytic leukemia
- venetoclax - Venetoclax in combination with azacitidine - Previously untreated acute myeloid leukemia

**High Cost Therapy Funding Program**

- 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 21, 2021.

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.

**July 2023** added general statement on hepatitis B testing

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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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