**Regimen Monograph**



## A - Regimen Name

# VENE(MNT) Regimen

**Venetoclax (Maintenance)**

**Disease Site**

Hematologic
Leukemia - Chronic Lymphocytic (CLL)

**Intent**

Palliative

**Regimen Category**

**Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

**Rationale and Uses**

For maintenance treatment after 6 cycles of VENE+RITU in patients with CLL

(Refer to EAP criteria)

**Supplementary Public Funding**

**venetoclax**
Exceptional Access Program (venetoclax - Treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) according to clinical criteria)

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## B - Drug Regimen

**As maintenance treatment after 6 cycles of VENE+RITU:**

| | | | |
|---|---|---|---|
| **venetoclax** | 400 mg | PO | Daily |

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## C - Cycle Frequency

**CONTINUOUS TREATMENT**

For a total of 24 months (from start of rituximab), unless disease progression or unacceptable toxicity occurs.

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** Low – No routine prophylaxis; PRN recommended

Also refer to CCO Antiemetic Recommendations.

**Other Supportive Care:**

- Consider supportive measures such as antimicrobials for signs of infection, and prophylactic use of G-CSF according to local guidelines.
- **Tumour lysis prophylaxis as clinically indicated.** For dose interruptions that last > 2 weeks, reassess for risk of TLS. Also refer to VENE+RITU for prophylaxis for TLS.

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## E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

**Refer to Interactions section for dosing recommendations when co-administered with **CYP3A or P-gp inhibitors** during **both ramp-up and daily dosing**.**

**Dosage with toxicity**

For dose interruptions that last > 2 weeks, 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.

| Toxicity/Event | Action* |
|---|---|
| Blood chemistry suggests TLS | Hold next day's dose.<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 | 1st occurrence:<br>Hold until ≤ Grade 1 or baseline; resume at same dose.<br><br>2nd and subsequent occurrence(s):<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>**G-CSF may be administered with venetoclax if clinically indicated. | |

**Hepatic Impairment**

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

**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 were 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 ethnicity**

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

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## F - Adverse Effects

Refer to venetoclax drug monograph(s) for additional details of adverse effects.

| Very common (≥ 50%) | Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|---|
| • Myelosuppression ± infection, bleeding (may be severe) | • Diarrhea<br>• Nausea, vomiting<br>• Fatigue<br>• Musculoskeletal pain | • Cough, dyspnea<br>• Edema<br>• Abdominal pain<br>• Rash, pruritus<br>• Secondary malignancy<br>• Headache<br>• Abnormal electrolyte(s) (↑ PO4, ↓/↑ K, ↓ Ca, ↓ Mg)<br>• Constipation<br>• Dizziness<br>• Mucositis | • Autoimmune hemolytic anemia<br>• Tumour lysis syndrome<br>• Multiple Organ Dysfunction Syndrome |

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## G - Interactions

Refer to venetoclax drug monograph(s) for additional details.

- Refer to the table below when co-administered with CYP3A inhibitors or P-gp inhibitors.
- Avoid concomitant use with both strong and moderate CYP3A4 inducers; consider alternative treatments.
- Avoid P-gp and BCRP substrates with a narrow therapeutic index (i.e. digoxin). If P-gp substrates must be used, administer at least 6 hours before venetoclax.
- Warfarin concentrations may be increased; monitor INR closely if used together.

**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 | **Contraindicated** | Avoid concomitant use. If unavoidable, reduce venetoclax dose to 100 mg or less. |
| Moderate CYP3A inhibitor | Avoid concomitant use. If unavoidable, reduce venetoclax dose by at least 50%. | |
| P-gp inhibitor | 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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## H - Drug Administration and Special Precautions

Refer to venetoclax drug monograph(s) for additional details.

**Administration:**

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.

**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.

**Warnings/Precautions**:

- Tumour lysis syndrome (see Premedication and Supportive Measures 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.

**Pregnancy/Lactation:**

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Do not breastfeed during this treatment. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Likely

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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

- CBC; Baseline, at each visit, and as clinically indicated
- Liver function tests; Baseline, at each visit, and as clinically indicated
- Blood chemistry and electrolytes (including potassium, uric acid, phosphorous, calcium, creatinine); At each visit, and as clinically indicated. Re-assess for risk of TLS after a dose interruption lasting > 2 weeks.
- 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 - Administrative Information

Outpatient prescription for home administration

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## K - References

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378:1107-20.

VENE+RITU regimen monograph. Ontario Health (Cancer Care Ontario).

Venetoclax drug monograph. Ontario Health (Cancer Care Ontario).

**May 2024** Modified Interactions and Pregnancy/Lactation sections

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## M - Disclaimer

***Regimen Abstracts***

*A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.*

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***Regimen Monographs***

*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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