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.

Also refer to Section G - Interactions for dosing when co-administered with CYP3A4 or P-gp inhibitors.

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. 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: Hold until ≤ Grade 1 or baseline; resume at same dose. 2nd and subsequent occurrence(s): 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.	

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 • Nausea, vomiting • Fatigue • Musculoskeletal pain	• Cough, dyspnea • Edema • Abdominal pain • Rash, pruritus • Secondary malignancy • Headache • Abnormal electrolyte(s) (↑ PO4, ↓/↑ K, ↓ Ca, ↓ Mg) • Constipation • Dizziness • Mucositis	• Autoimmune hemolytic anemia • Tumour lysis syndrome • Multiple Organ Dysfunction Syndrome

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G - Interactions

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

- Strong CYP3A4 inhibitors are **contraindicated during initiation and ramp-up phase**. Avoid concomitant use at steady state. If concomitant use is required, reduce venetoclax dose to 100 mg or less; resume previous venetoclax dose 2 to 3 days after stopping the inhibitor.
- Avoid concomitant use of moderate CYP3A4 inhibitors; reduce venetoclax dose by at least 50% if concomitant use is unavoidable. Resume previous venetoclax dose 2 to 3 days after stopping the inhibitor.
- When used concomitantly with P-gp inhibitors, reduce the venetoclax dose by at least 50%; resume previous venetoclax dose 2 to 3 days after stopping the inhibitor. Venetoclax dose adjustment is not required when co-administered with azithromycin.
- 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 must be

used, administer at least 6 hours before venetoclax.
- Warfarin concentrations may be increased; monitor INR closely if used together.

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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:

- 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 (and for at least **12 months** after the last dose of rituximab).

- Breastfeeding is not recommended during treatment with venetoclax (and until rituximab drug levels are no longer detectable).
- 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.

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 2021 New regimen monograph

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M - Disclaimer

Regimen Abstracts

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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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