Regimen Monograph

A - Regimen Name

VENE Regimen

Venetoclax

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

Treatment for relapsed refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma, as the second or subsequent line of therapy in patients who have experienced treatment failure or unacceptable toxicities to at least 1 prior line of therapy.

(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

Venetoclax dose ramp-up period (5 weeks total):

venetoclax	20 mg	PO	Daily x 1 week
venetoclax	50 mg	PO	Daily x 1 week
venetoclax	100 mg	PO	Daily x 1 week
venetoclax	200 mg	PO	Daily x 1 week
venetoclax	400 mg	PO	Daily x 1 week

THEN

venetoclax	400 mg	PO	Daily

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

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

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** (i.e. adequate hydration and anti-hyperuricemic agents) prior to and during ramp-up phase **is required for all patients.**

Prophylaxis for TLS:

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 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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E - Dose Modifications

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

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

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**.**

Dosage with toxicity

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>
<tr><th>Toxicity/Event</th><th>Action*</th></tr>
<tr><td>Blood chemistry suggests TLS</td><td>Hold next day's dose.
If resolved within 24-48 hours; resume at same dose.</td></tr>
<tr><td>Clinical TLS or blood chemistry changes for ≥ 48 hours</td><td>Hold until resolved; resume at a reduced dose (see table above) and follow TLS prophylaxis.</td></tr>
<tr><td>Any Grade 3 or 4 non-hematological</td><td rowspan="3"><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.</td></tr>
<tr><td>≥ Grade 3 neutropenia** with infection or fever</td></tr>
<tr><td>Grade 4 hematological toxicities (except lymphopenia)</td></tr>
<tr><td colspan="2">*For dose reductions to < 100 mg for > 2 weeks, consider discontinuing.
**G-CSF may be administered with venetoclax if clinically indicated.</td></tr>
</table>

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

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 CYP3A inhibitors** are **contraindicated during initiation and ramp-up phase**.
- 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

- 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 - Administrative Information

Outpatient prescription for home administration

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K - References

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.

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.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

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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