Regimen Monograph

A - Regimen Name

ZANU Regimen

Zanubrutinib

Disease Site

Hematologic
Lymphoma - Non-Hodgkin's Low Grade

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 the treatment of relapsed or refractory Waldenström macroglobulinemia (WM), in patients who have at least 1 prior line of treatment for WM, have good performance status, have not progressed on another BTK inhibitor for WM, and have no disease transformation to another form of cancer
(Funded by EAP)

- For the treatment of relapsed/refractory mantle cell lymphoma
(**NOT** funded by EAP)

Supplementary Public Funding	**zanubrutinib** Exceptional Access Program (zanubrutinib - For the treatment of relapsed or refractory Waldenström Macroglobulinemia, according to clinical criteria) (EAP Website)

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B - Drug Regimen

zanubrutinib	320 mg	PO	Once Daily*
OR			
zanubrutinib	160 mg	PO	BID^

*For WM, both dosing schedules are funded. Once-daily dosing is preferred. (CADTH)

^For MCL, there are more clinical data to support twice-daily dosing; once-daily dosing may be given as an alternative. (CADTH)

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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: Minimal – 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:

- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.
- Consider prophylaxis according to local practices for patients at an increased risk for opportunistic infections.
- Patients should be advised to use adequate sun protection (prevention of secondary skin cancers).

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E - Dose Modifications

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

Consider withholding zanubrutinib for 3-7 days pre-and post-surgery based on a risk-benefit analysis (e.g. surgery type, risk of bleeding).

Refer to Interactions Section for dosing recommendations when co-administered with CYP 3A4 inducers or inhibitors.

Dosage with toxicity

Dose Levels	Once Daily Zanubrutinib Dosing	Twice Daily Zanubrutinib Dosing
0	320 mg once daily	160 mg BID
-1	160 mg once daily	80 mg BID
-2	80 mg **once daily**	
-3	Discontinue	

Asymptomatic lymphocytosis should not be regarded as a toxicity; continue taking zanubrutinib.

Toxicity	Occurrence	Action
Febrile neutropenia OR Grade 4 neutropenia, lasting > 10 days	First	Hold until toxicity is Grade ≤ 1 or baseline. Resume at the same dose.
	Second and Third	Hold until toxicity is Grade ≤ 1 or baseline. Resume at next lower dose level.
	Fourth	Discontinue.
Grade 3 thrombocytopenia, with significant bleeding OR Grade 4 thrombocytopenia, lasting > 10 days	First	Hold until toxicity is Grade ≤ 1 or baseline. Resume at the same dose.
	Second and Third	Hold until toxicity is Grade ≤ 1 or baseline. Resume at next lower dose level.
	Fourth	Discontinue.
Intracranial hemorrhage	Any	Discontinue.
Pneumonitis	Any	Hold and investigate. Discontinue if confirmed.
Other Grade ≥ 3 non-hematologic toxicities	First	Hold until toxicity is Grade ≤ 1 or baseline. Resume at the same dose.
	Second and Third	Hold until toxicity is Grade ≤ 1 or baseline. Resume at next lower dose level.
	Fourth	Discontinue.

Hepatic Impairment

Monitor closely for toxicity in patients with hepatic impairment.

Hepatic Impairment	Zanubrutinib Dose
Mild	No dose adjustment required.
Moderate	
Severe	80 mg BID

Renal Impairment

Creatinine Clearance	Zanubrutinib dose
≥ 30	No dose adjustment required.
< 30 (or on dialysis)	Limited data available; monitor for toxicity.

Dosage in the Elderly

No dose adjustment is necessary due to age. No differences in safety or efficacy were observed between patients ≥ 65 years and younger patients.

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F - Adverse Effects

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

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Musculoskeletal pain • Myelosuppression ± infection (may be severe)	• Hemorrhage (may be severe) • Diarrhea • Fatigue • Rash • Constipation • Headache • Nausea, vomiting • Cough, dyspnea • Dizziness • Hypertension	• Atrial fibrillation • Pleural effusion • Pneumonitis • Tumour lysis syndrome (mostly in CLL) • Secondary malignancy

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G - Interactions

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

- Avoid concomitant use with strong or moderate CYP3A inducers. Consider alternatives with less CYP3A induction. If concomitant use with a moderate CYP3A inducer is required, ↑ zanubrutinib to 320 mg twice daily during co-administration; monitor closely for toxicity.
- Reduce zanubrutinib to 80 mg **once daily** if co-administered with a **strong** CYP3A inhibitor. Hold dose for toxicities. Resume previous dose after inhibitor is discontinued.
- Reduce zanubrutinib to 80 mg **twice daily** if co-administered with a **moderate** CYP3A inhibitor. Modify dose for toxicities. Resume previous dose after inhibitor is discontinued.
- Consider the benefits and risks of using anticoagulant or antiplatelet therapy. Monitor for signs of bleeding.

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H - Drug Administration and Special Precautions

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

Administration

- Administer zanubrutinib with or without food.
- Capsules should be swallowed whole with a glass of water. Do not crush, dissolve or open capsules.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during zanubrutinib treatment.
- If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Store at room temperature (15°C-30°C), in original bottle.

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components

Warnings/Precautions

- The following patients were excluded from clinical trials; consider the benefits and risks of using zanubrutinib in patients with:
  - a history of severe bleeding disorder, spontaneous bleeding, stroke, intracranial hemorrhage, or who require warfarin or other vitamin K antagonists
  - active or clinically significant cardiovascular disease
  - moderate and severe cytopenias
  - active fungal, bacterial and/or viral infection, or with documented HIV infection, active hepatitis B or C
  - severe or debilitating pulmonary disease
- Serious bleeding events have occurred with zanubrutinib. Consider withholding zanubrutinib for 3-7 days pre-and post-surgery based on a risk-benefit analysis that includes surgery type and risk of bleeding.
- Use caution in patients with cardiac risk factors, hypertension, and acute infections as these patients may be at an increased risk for cardiovascular adverse effects.

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.
- Breastfeeding is not recommended during treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

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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, monthly at the beginning of treatment, then less frequently as clinically indicated
- Liver function tests; Baseline, monthly at the beginning of treatment, then less frequently as clinically indicated
- Renal function tests, electrolytes; Baseline, monthly at the beginning of treatment, then less frequently as clinically indicated
- ECG; Baseline and as clinically indicated. Monitor for symptoms of arrhythmia during treatment.
- Clinical toxicity assessment for bleeding, infections, pneumonitis, tumour lysis syndrome (especially for CLL), and secondary malignancies (including skin); 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

CADTH reimbursement recommendation: Zanubrutinib (Waldenström macroglobulinemia), December 2021.

CADTH reimbursement review: Zanubrutinib (mantle cell lymphoma), September 2022.

Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. Clin Cancer Res 2020 Aug 15;26(16):4216-24.

Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood 2020 Oct 29;136(18):2038-50.

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

March 2024 Expanded into full regimen monograph

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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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