Drug Monograph

A - Drug Name

zanubrutinib

COMMON TRADE NAME(S): Brukinsa®

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B - Mechanism of Action and Pharmacokinetics

Zanubrutinib is an inhibitor of Bruton's tyrosine kinase (BTK), a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Zanubrutinib forms a covalent bond with a cysteine residue in the active site of BTK, leading to inhibition of BTK activity and ultimately inhibits proliferation of malignant B-cells.

Absorption	T max	2 hours
	Effects with food	Administration of a high-fat meal did not appear to have any clinically significant effects on C_{max} and AUC.
Distribution	Exposure increased proportionally over a dosage range from 40 mg to 320 mg. Limited systemic accumulation was observed following repeated administration.	
	Cross blood brain barrier?	Yes (based on case series)
	PPB	94%
Metabolism	Zanubrutinib is metabolized mainly by CYP3A.	

Elimination	Half-life	2 to 4 hours (mean)
	Feces	87% (38% unchanged)
	Urine	8% (< 1% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL)
- Marginal zone lymphoma (MZL)
- Chronic lymphocytic leukemia (CLL)
- Follicular lymphoma (FL)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were reported in ≥ 10% of relapsed/refractory or treatment-naïve WM patients with MYD88 mutation in a Phase III study. It also includes severe or life-threatening adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (5%) (2% severe)	E
	Hypertension (11%) (6% severe)	E
Dermatological	Rash (18%)	E
Gastrointestinal	Constipation (16%)	E
	Diarrhea (21%)	E

	Nausea, vomiting (15%)	E
General	Fatigue (19%)	E
Hematological	Hemorrhage (21%) (5% severe)	E
	Myelosuppression ± infection (25%) (16% severe) (including viral reactivation)	E
Metabolic / Endocrine	Tumor lysis syndrome (<10%) (mostly in CLL)	I E
Musculoskeletal	Musculoskeletal pain (30%)	E
Neoplastic	Secondary malignancy (12%) (including 7% skin)	D L
Nervous System	Dizziness (13%)	E
	Headache (15%)	E
Respiratory	Cough, dyspnea (14%)	E
	Pleural effusion (2%)	E
	Pneumonitis (1%)	E

* "*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 zanubrutinib include musculoskeletal pain, myelosuppression ± infection, hemorrhage, diarrhea, fatigue, rash, constipation, headache, nausea, vomiting, cough and dyspnea.

New primary malignancies, including skin cancer and non-skin carcinoma, have been reported. The most frequent was skin cancer (i.e., basal cell carcinoma, squamous cell carcinoma of skin, and malignant melanoma).

Bleeding, including serious and fatal events, has occurred. Grade $\geq$ 3 events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported.

Serious infections, including fatal events, have been reported. **Pneumonia** was the most frequent. Hepatitis B virus (HBV), varicella zoster reactivation, and opportunistic infections have also occurred.

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E - Dosing

Refer to protocol by which the 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.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

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

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).

Adults:

Oral: 320 mg once daily OR 160 mg BID

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.

Dosage with 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

Dosage with 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.

Dosage based on gender:

Sex does not have clinically meaningful effects on the pharmacokinetics (PK) of zanubrutinib.

Dosage based on ethnicity:

Race does not have clinically meaningful effects on the PK of zanubrutinib.

Children:

The safety and efficacy of zanubrutinib have not been established in children < 18 years of age.

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F - Administration Guidelines

- 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 given in combination with obinutuzumab, zanubrutinib should be taken prior to the obinutuzumab infusion.
- 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.

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G - Special Precautions

Contraindications:

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

Other 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.

Other Drug Properties:

- Carcinogenicity:
  Although carcinogenicity studies have not been conducted, serious and fatal new primary malignancies have been reported.

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Zanubrutinib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **1 week** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment, and for at least **2 weeks** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Zanubrutinib is metabolized mainly by CYP3A. Zanubrutinib may reduce exposure of CYP2C19 and CYP3A4 substrates (e.g. omeprazole, by 36%; midazolam, by 47%), or increase exposure of P-gp substrates (e.g. digoxin, 11%). *In vitro*, zanubrutinib is a weak inducer of CYP2B6 and is likely to be a substrate of P-gp, but is neither a substrate nor an inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort)	↓ zanubrutinib concentration (by 93% with rifampin) and/or efficacy	↑ metabolism of zanubrutinib	Avoid concomitant use with strong CYP3A inducers. Consider alternatives with less CYP3A induction.
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	↓ zanubrutinib concentration and/or efficacy	↑ metabolism of zanubrutinib	Avoid concomitant use with moderate CYP3A inducers. Consider alternative agents with less CYP3A induction. If concomitant use cannot be avoided, ↑ zanubrutinib to 320 mg twice daily during co-administration; monitor closely for toxicity.
Strong CYP3A inhibitors (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, lopinavir, ritonavir)	↑ zanubrutinib concentration (by 278% with itraconazole) and/or toxicity	↓ metabolism of zanubrutinib	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.
Moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, fruit or juice from	↑ zanubrutinib concentration and/or toxicity	↓ metabolism of zanubrutinib	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.

grapefruit, Seville oranges or starfruit)			
Antiplatelets or Anticoagulants	↑ risk of bleeding	Additive	Consider the benefits and risks of using anticoagulant or antiplatelet therapy. Monitor for signs of bleeding.

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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
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, symptoms of arrhythmia	Baseline and as clinically indicated
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 - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- zanubrutinib - For the treatment of relapsed or refractory Waldenström Macroglobulinemia, according to clinical criteria
- zanubrutinib - For the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; and for the treatment of adult patients with previously untreated CLL.

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K - References

ASCO Guidelines. Emetic Risk of Single Oral Antineoplastic Agents in Adults. 2020.

NCCN Guidelines®: Antiemesis. May 24, 2023.

Product monograph: Brukinsa® (zanubrutinib). BeiGene Switzerland GmbH. January 31, 2024.

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.

Summary of Product Characteristics. Brukinsa 80 mg hard capsules (zanubrutinib). BeiGene UK Ltd. January 6, 2023.

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.

Zhang Y, Li Y, Zhuang Z, Wang W, et al. Preliminary Evaluation of Zanubrutinib-Containing Regimens in DLBCL and the Cerebrospinal Fluid Distribution of Zanubrutinib: A 13-Case Series. Front Oncol. 2021 Dec 24;11:760405.

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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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