DRUG NAME: Zanubrutinib

SYNONYM(S): BGB-3111 [1]

COMMON TRADE NAME(S): BRUKINSA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Zanubrutinib is an orally administered, highly-specific, small molecule inhibitor of Bruton's tyrosine kinase (BTK). BTK is an integral part of the B-cell antigen receptor (BCR) pathway, which is associated with the pathogenesis of several B-cell malignancies. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. Zanubrutinib inhibits malignant B-cell proliferation and reduces tumour growth. [1-4]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2 hours; no clinically significant difference in zanubrutinib AUC or C_{max} were observed following administration with high fat meals [5]	
Distribution	blood-to-plasma ratio is 0.7 to 0.8	
	cross blood brain barrier?	no information found
	volume of distribution	522 L
	plasma protein binding	94%
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily fecal elimination	
	urine	8% (<1% unchanged)
	feces	87% (38% unchanged)
	terminal half life	2-4 h
	clearance	128 L/h
Elderly	no clinically significant difference	
Sex	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference [2-4] unless specified otherwise.

USES:

Primary uses:

*Waldenström's macroglobulinemia
*Lymphoma, mantle cell
*Lymphoma, non-Hodgkin
*Leukemia, chronic lymphocytic

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- zanubrutinib dose adjustment may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway [2,3]
- patients with pre-existing ***hepatic impairment*** may require starting dose reduction [2,3]
- ***risk of bleeding*** may be increased with co-administration of anticoagulants or medications that inhibit platelet function; consider withholding treatment for 3-7 days pre- and post-surgery [2,3]
- ***atrial fibrillation*** *and* ***atrial flutter*** are reported; risk may be increased in patients with cardiac risk factors, hypertension, or acute infection [2,3]
- ***opportunistic infections***, including ***hepatitis B reactivation***, are reported [2,3]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis*** [6]

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary primary malignancies have been reported with zanubrutinib. [2]

Mutagenicity: Not mutagenic in Ames test. Zanubrutinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. [2,3]

Fertility: In animal studies, morphological abnormalities in sperm were observed at exposures approximately 9 times higher than those seen following human clinical exposure. [2,3]

Pregnancy: In animal studies, zanubrutinib caused embryo-fetal developmental toxicity. Heart malformations, decreased body weights, and ocular findings (e.g., cataract, protruding eye) were observed at exposures approximately 4-5 times higher than those seen following human clinical exposure. Increased post-implantation loss was observed at exposures approximately 9 times higher than those seen following human clinical exposure. Pregnancy tests are recommended prior to starting treatment for female patients of childbearing potential. Contraception is recommended during treatment and for at least one week after the last dose in female patients of childbearing potential. In male patients with female partners of childbearing potential, contraception is recommended for at least three months after the last dose. Zanubrutinib may reduce the effectiveness of hormonal contraceptives via CYP 3A4 induction; use of an additional contraceptive measure is recommended. [2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for two weeks following the last dose. [2,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. [7,8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (14-30%, severe 5-8%)
	febrile neutropenia (3-8%)
	leukopenia (25%, severe 5%)
	lymphocytosis (41%, severe 16%)
	neutropenia (17-54%, severe 13-26%); see paragraph following **Side Effects** table
	thrombocytopenia (15-44%, severe 4-11%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	***atrial fibrillation/atrial flutter*** (3%, severe 1%)
	cardiomegaly (1%); fatal events reported
	palpitations (<10%)
	sinus bradycardia (<10%)
ear and labyrinth	tinnitus (<10%)
eye	blurry vision (<10%)
gastrointestinal	*emetogenic potential:* low [9]
	abdominal pain (10-14%, severe 2%)
	angina bullosa hemorrhagica (<10%)
	constipation (13-16%)
	diarrhea (22-25%, severe 1-3%)
	dry mouth (<10%)
	dyspepsia (<10%)
	gastroesophageal reflux disease (<10%)
	nausea (13-18%)
	stomatitis (<10%)
	vomiting (12%)
general disorders and administration site conditions	chest pain (<10%)
	chills (<10%)
	fatigue (11-31%, severe 1-3%)
	gait disturbance (<10%)
	influenza-like illness (<10%)
	peripheral edema (12%)
	pyrexia (16%, severe 4-5%)
infections and infestations	conjunctivitis (<10%)
	cystitis (<10%)
	infections (74%, severe 27%); see paragraph following **Side Effects** table
	nasopharyngitis (<10%)
	oral herpes (<10%)
	pneumonia (4-15%, severe 4-10%); fatal events reported
	sinusitis (<10%)
	skin infection (<10%)
	tonsillitis (<10%)
	upper respiratory infection (17-47%, severe 1-3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	urinary tract infection (11%, severe <3%)
investigations	alkaline phosphatase increase (20%)
	ALT increase (13-30%, severe 1%)
	AST increase (11%)
	bilirubin increase (11-26%, severe 1%)
	calcium decrease (23-27%, severe 2%)
	creatinine increase (15-34%, severe 1%)
	glucose increase (26-54%, severe 1-5%)
	phosphate decrease (20-27%, severe 2-3%)
	potassium increase (24%, severe 2%)
	urate increase (14-31%, severe 3%)
	weight decrease (<10%)
metabolism and nutrition	appetite decrease (<10%)
	dehydration (<10%)
	hypokalemia (14%, severe 2%)
musculoskeletal and connective tissue	joint swelling (<10%)
	muscle spasms (10%)
	muscle weakness (<10%)
	musculoskeletal pain (14-45%, severe 1-9%)
	pain in extremity (<10%)
neoplasms	***second primary malignancies*** (14%), including skin cancer (9%); see paragraph following **Side Effects** table
nervous system	dizziness (13%, severe 1%)
	headache (4-18%, severe 1%)
	paresthesia (<10%)
	peripheral sensory neuropathy (<10%)
	syncope (<10%)
psychiatric	anxiety (<10%)
	depression (<10%)
	insomnia (<10%)
renal and urinary	hematuria (<10%)
	nocturia (<10%)
	urinary retention (<10%)
respiratory, thoracic and mediastinal	cough (10-16%)
	dyspnea (14%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dysphonia (<10%)
	epistaxis (<10%)
	interstitial lung disease (2%)
	pleural effusion (3%)
skin and subcutaneous tissue	bruising (14-24%)
	hyperhidrosis (<10%)
	petechiae (<10%)
	pruritus (11%, severe 1%)
	purpura (<10%)
	rash (16-36%)
	skin lesion (<10%)
	skin ulcer (<10%)
vascular	***hemorrhage*** (10-54%, severe 1-4%); see paragraph following **Side Effects** table
	hypertension (12-14%, severe 3-9%)

Adapted from standard reference [2-4] unless specified otherwise.

Hemorrhage, including serious and fatal hemorrhagic events, has been reported in up to 54% of patients. Grade 3 or higher bleeding events include intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax. Patients with history of severe bleeding disorder, spontaneous bleeding, stroke, intracranial hemorrhage, or those receiving antiplatelet or anticoagulant therapies may be at increased risk of a bleeding event. Manage bleeding events with supportive measures, including transfusion, and specialized care as clinically necessary. Treatment interruption and/or discontinuation may be required. [2,3]

Infections, including bacterial, viral, fungal, and opportunistic infections are frequently reported with zanubrutinib. Approximately 20% of reported infections are associated with concurrent neutropenia. Fatal infections have been reported in 2.5% of patients. Consider prophylaxis in patients who are at increased risk for infection. [2,3]

Second primary malignancies, including serious and fatal malignancies, have been reported. Skin cancer, the most frequently occurring second primary malignancy, was reported in 9% of patients and can include basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Monitor for the appearance of suspicious skin lesions and advise patients on appropriate sun protection measures. [2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
clarithromycin [5]	101% increase in C_{max} and 92% increase in AUC of zanubrutinib	strong inhibition of CYP 3A4 by voriconazole	reduce zanubrutinib dose to 80 mg PO once daily and monitor for zanubrutinib toxicity
digoxin [2-4]	34% increase in C_{max} and 11% increase in AUC of digoxin	inhibition of P-gp by zanubrutinib	monitor digoxin levels and check for signs of digoxin toxicity

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AGENT	EFFECT	MECHANISM	MANAGEMENT
diltiazem [2]	62% increase in C_{max} and 62% increase in AUC of zanubrutinib	moderate inhibition of CYP 3A4 by diltiazem	reduce zanubrutinib dose to 80 mg PO twice daily and monitor for zanubrutinib toxicity
fluconazole [5]	81% increase in C_{max} and 88% increase in AUC of zanubrutinib	moderate inhibition of CYP 3A4 by fluconazole	reduce zanubrutinib dose to 80 mg PO twice daily and monitor for zanubrutinib toxicity
gastric acid reducing agents [2,3]	no clinically significant difference in pharmacokinetics of zanubrutinib	pH-dependent solubility of zanubrutinib	none required
grapefruit juice [2,3]	may increase plasma level of zanubrutinib	may inhibit CYP 3A4 metabolism of zanubrutinib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of zanubrutinib therapy
itraconazole [2,3]	157% increase in C_{max} and 278% increase in AUC of zanubrutinib	strong inhibition of CYP 3A4 by itraconazole	reduce zanubrutinib dose to 80 mg PO once daily and monitor for zanubrutinib toxicity
midazolam [2-4]	30% decrease in C_{max} and 47% decrease in AUC of midazolam	induction of CYP 3A4 by zanubrutinib	none required; considered unlikely to be clinically significant
omeprazole [2-4]	20% decrease in C_{max} and 36% decrease in AUC of omeprazole	induction of CYP 2C19 by zanubrutinib	none required; considered unlikely to be clinically significant
rifabutin [5]	48% decrease in C_{max} and 44% decrease in AUC of zanubrutinib	moderate induction of CYP 3A4 by rifabutin	avoid concurrent use; if concurrent use cannot be avoided, increase zanubrutinib dose to 320 mg twice daily and monitor for zanubrutinib toxicity
rifampin [2,3]	92% decrease in C_{max} and 93% decrease in AUC of zanubrutinib	strong induction of CYP 3A4 by rifampin	avoid concurrent use
rosuvastatin [5]	no clinically significant difference in pharmacokinetics of rosuvastatin	possible inhibition of BCRP by zanubrutinib	none required
voriconazole [5]	229% increase in C_{max} and 230% increase in AUC of zanubrutinib	strong inhibition of CYP 3A4 by voriconazole	reduce zanubrutinib dose to 80 mg PO once daily and monitor for zanubrutinib toxicity
warfarin [5]	no clinically significant difference in pharmacokinetics of warfarin	possible induction of CYP 2C9 by zanubrutinib	none required

Zanubrutinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of zanubrutinib. If coadministration with *moderate* CYP 3A4 inhibitors cannot be avoided, reduce zanubrutinib dose to 80 mg PO twice daily. If coadministration with *strong* CYP 3A4 inhibitors cannot be avoided, reduce zanubrutinib dose to 80 mg PO once daily. If the CYP 3A4 inhibitor is discontinued, zanubrutinib may be resumed at its prior dose. [2,3]

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CYP 3A4 ***inducers*** may decrease the plasma concentration of zanubrutinib. Avoid concurrent use with *moderate* and *strong* CYP 3A4 inducers. [2,3]

Zanubrutinib is a weak inducer of CYP 2B6 and CYP 2C19 and a substrate of P-gp *in vitro*; clinical significance is unknown. [2,3]

SUPPLY AND STORAGE:

Oral: Innomar Strategies Inc. supplies zanubrutinib as 80 mg hard gelatin capsules and 160 mg film-coated tablets. Tablets are scored and contain lactose. Store at room temperature. [2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral [1,5,10-12]*:*	***160 mg*** (range 80-160 mg) ***PO twice daily**** OR ***320 mg*** (range 80-320 mg) ***PO once daily**** Administer with food or on an empty stomach. Do not take with grapefruit or grapefruit juice. *dose modification may be required for some drug interactions
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required [2,3] CrCl 15-29 mL/min: no adjustment required; monitor for toxicity[2] CrCl <15 mL/min: no information found; monitor for toxicity [2,3] calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure: [2,3]	mild/moderate impairment: no adjustment required; monitor for toxicity severe impairment: 80 mg PO twice daily; monitor for toxicity
Dosage in dialysis: [2,3]	no information found; monitor for toxicity

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Children: safety and efficacy have not been established [2]

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