PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr BRUKINSA®

zanubrutinib capsules

Capsules, 80 mg, Oral

Bruton's Tyrosine Kinase (BTK) Inhibitor

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TABLE OF CONTENTS

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4
- 1.1 Pediatrics 4
- 1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 4

4 DOSAGE AND ADMINISTRATION 4
- 4.1 Dosing Considerations 4
- 4.2 Recommended Dose and Dosage Adjustment 4
- 4.3 Administration 6
- 4.4 Missed Dose 6

5 OVERDOSAGE 6

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 6

7 WARNINGS AND PRECAUTIONS 7
- 7.1 Special Populations 9
- 7.1.1 Pregnant Women 9
- 7.1.2 Breast-feeding 9
- 7.1.3 Pediatrics 9
- 7.1.4 Geriatrics 10

8 ADVERSE REACTIONS 10
- 8.1 Adverse Reaction Overview 10
- 8.2 Clinical Trial Adverse Reactions 10
- 8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 13

9 DRUG INTERACTIONS 14
- 9.1 Overview 14
- 9.2 Drug-Drug Interactions 14
- 9.3 Drug-Food Interactions 16
- 9.4 Drug-Herb Interactions 16

10 ACTION AND CLINICAL PHARMACOLOGY 16
- 10.1 Mechanism of Action 16
- 10.2 Pharmacodynamics 17
- 10.3 Pharmacokinetics 17

11 STORAGE, STABILITY AND DISPOSAL 18

12 SPECIAL HANDLING INSTRUCTIONS 18

13 PHARMACEUTICAL INFORMATION 19

14 CLINICAL TRIALS 19
14.1 Trial Design and Study Demographics 19
14.2 Study Results 21
15 Microbiology 22
16 NON-CLINICAL TOXICOLOGY 22
PATIENT MEDICATION INFORMATION 24

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BRUKINSA (zanubrutinib) is indicated:

- for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

1.1 Pediatrics

Pediatrics (<18 years of age): No safety and efficacy data are available; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years. See 7 WARNINGS AND PRECAUTIONS, Special Populations.

2 CONTRAINDICATIONS

BRUKINSA is contraindicated in patients who are hypersensitive to zanubrutinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with BRUKINSA should be initiated and supervised by a qualified physician experienced in the use of anticancer therapies.
- Serious Hemorrhage: (see 7 WARNINGS AND PRECAUTIONS, Vascular).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Avoid concomitant use with moderate or strong CYP3A inducers (see 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose
The recommended total daily oral dose of BRUKINSA is 320 mg. BRUKINSA may be taken as either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily.

Treatment with BRUKINSA should continue until disease progression or unacceptable toxicity.

Dosage Adjustment
Recommended dose modifications of BRUKINSA for Grade ≥ 3 adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modification for Adverse Reaction

Event	Adverse Reaction Occurrence	Dose Modification (Starting Dose: 160 mg twice daily)
≥ Grade 3 non-hematological toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting >10 consecutive days) Grade 4 thrombocytopenia (lasting > 10 consecutive days)	First	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg twice daily or 320 mg once daily
	Second	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg twice daily or 160 mg once daily
	Third	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue BRUKINSA

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking zanubrutinib.

Recommended dose modification for use with CYP3A inhibitors or inducers are provided in Table 2.

Table 2: Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended Dose
Inhibition	Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions
	Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions
Induction	Strong and moderate CYP3A inducer	Avoid concomitant use; Consider alternative agents with less CYP3A induction

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA.

Special Populations

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose modification is necessary based on age (see 10 ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: No dose modification is recommended in patients with mild to moderate renal impairment (CrCl ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis.

Hepatic Impairment: No dose modification is recommended in patients with mild or moderate hepatic impairment.

The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. Monitor closely for BRUKINSA adverse reactions in patients with hepatic impairment.

4.3 Administration

BRUKINSA capsules should be swallowed whole with water, BRUKINSA can be taken with or without food. The capsule should not be chewed, dissolved, or opened. BRUKINSA must not be taken with grapefruit juice, grapefruit and/or Seville oranges.

4.4 Missed Dose

If a dose of BRUKINSA 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.

5 OVERDOSAGE

There is no specific treatment for BRUKINSA overdose. For patients who experience overdose closely monitor and provide appropriate supportive treatment.

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule / 80 mg	ammonium hydroxide (trace), colloidal silicon dioxide, croscarmellose sodium, dehydrated ethanol (trace), gelatin, iron

		oxide black (trace), isopropyl alcohol (trace), magnesium stearate, microcrystalline cellulose, n-butyl alcohol (trace), propylene glycol (trace), purified water (trace), shellac glaze in ethanol (trace), sodium lauryl sulphate, titanium dioxide.

Description
Size 0 hard gelatin capsule with a white to off-white opaque body and cap, marked in black ink with 'ZANU 80'.

Packaging
White high density polyethylene (HDPE) plastic bottle, capped with a child-resistant polypropylene closure containing 120 capsules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

Carcinogenesis and Mutagenesis
Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma have occurred in 12% patients with hematological malignancies treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma, squamous cell carcinoma of skin, and melanoma), reported in 8% of patients. Monitor patients for skin cancer and advise patients to use sun protection.

Cardiovascular
Patients with active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia, class 3 or 4 congestive heart failure or recent myocardial infarction, were excluded from clinical trials of BRUKINSA.

Atrial Fibrillation and Flutter
Atrial fibrillation and atrial flutter have occurred in 2% of patients with hematological malignancies treated with BRUKINSA monotherapy. This risk may be increased in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 and above events were reported in 0.6% of patient. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and manage as appropriate.

Driving and Operating Machinery
No specific studies have been conducted to evaluate the influence of BRUKINSA treatment on the ability to drive or operate heavy machinery. Fatigue, dizziness, and asthenia have been reported in some patients taking BRUKINSA and should be considered when assessing a patient's ability to drive or operate machines.

Hematologic
Cytopenias
Grade 3 or 4 neutropenia (27%, including febrile neutropenia), thrombocytopenia (10%) and

anemia (7%) based on laboratory measurements were reported in patients with hematologic malignancies treated with BRUKINSA monotherapy (see 8 ADVERSE REACTIONS). Monitor complete blood counts regularly during treatment (see Monitoring and Laboratory Tests). Reduce dose, interrupt or discontinue treatment as necessary (See 4 DOSAGE AND ADMINISTRATION) and treat using growth factors or transfusion as necessary.

Immune

Infections

Serious and fatal infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 26%of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) or varicella zoster reactivation (herpes zoster) have occurred.

Monitor patients for signs and symptoms of infection and treat promptly and appropriately. Consider prophylaxis according to standard of care in patients who are at increased risk for infections.

Monitoring and Laboratory Tests

- Monitor complete blood counts as per routine clinical practice.
- Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) of atrial fibrillation and atrial flutter and obtain an echocardiogram (ECG) as appropriate.
- Monitor patients for the appearance of skin cancers.
- Monitor patients for signs and symptoms of infection and treat as medically appropriate.
- Monitor patients for signs of bleeding.

Peri-Operative Considerations

Consider the benefit-risk of withholding BRUKINSA for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Reproductive Health: Female and Male Potential

Fertility

No data on the effects of BRUKINSA on fertility in humans are available. No effects of zanubrutinib on fertility or reproductive capacities were observed in male or female rats, but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity).

Teratogenic Risk

BRUKINSA can cause harm to the developing fetus and loss of pregnancy (See 7.1.1 Pregnant Women). Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for at least 1 week after the last dose of BRUKINSA. Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA.

Advise men to avoid fathering a child while receiving BRUKINSA and for at least 3 months following the last dose of BRUKINSA.

Respiratory

Interstitial Lung Disease (ILD)

Cases of suspected ILD have occurred in 0.8% of patients with hematological malignancies

treated with BRUKINSA monotherapy. However, none were confirmed by biopsy. Monitor patients for signs and symptoms of ILD. Advise patients to report promptly any new or worsening respiratory symptoms. If ILD is suspected, interrupt BRUKINSA and treat promptly and appropriately. If ILD is confirmed, discontinue BRUKINSA.

Vascular

Hemorrhage

Serious and fatal hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 4% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 53% of patients with hematological malignancies treated with BRUKINSA monotherapy.

BRUKINSA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Patients were excluded from BRUKINSA studies if they had recent history of stroke or intracranial hemorrhage, or if they required warfarin or other vitamin K antagonists.

Patients should be monitored for signs of bleeding. Bleeding events should be managed with supportive measures, including transfusions, and specialized care as needed. Reduce dose, interrupt or discontinue treatment as necessary (See 4 DOSAGE AND ADMINISTRATION). For any intracranial hemorrhage, treatment should be discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of BRUKINSA in pregnant women. Based on findings in animals, zanubrutinib may cause fetal harm when administered to pregnant women (see 16 NON-CLINICAL TOXICOLOGY). Women of child-bearing potential must use highly effective contraceptive measures while taking BRUKINSA and at least for one week after stopping treatment. Women who use hormonal methods of birth control must add a barrier method. If BRUKINSA is used during pregnancy or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breast-feeding

It is unknown if BRUKINSA is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of BRUKINSA in children and adolescents aged less than 18 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 779 patients in clinical trials of BRUKINSA, 51.9% were 65 years of age or older, and 19.5% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of BRUKINSA is based on pooled data from 779 patients with B-cell malignancies treated with BRUKINSA in clinical trials.

The most common adverse reactions (≥ 10%) were neutropenia, thrombocytopenia, upper respiratory tract infection, anemia, rash, musculoskeletal pain, diarrhea, cough, contusion, pneumonia (grouped terms), urinary tract infection, hemorrhage (grouped terms), and hematuria.

Overall, 18% of patients experienced serious adverse reactions. The most frequently reported serious adverse reactions (≥ 2%) were pneumonia (10%) and hemorrhage (2.1%).

Deaths due to adverse events within 30 days of the last dose were reported in 3% of patients. The most common treatment-emergent adverse events leading to death were infection (2%, with infection-related adverse drug reactions leading to death of 0.9%) and cardiac events (<1%).

Of the 779 patients treated with BRUKINSA, 47 (6%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (1.3%). Adverse reactions leading to dose reduction occurred in 5.3% of patients. The most frequent adverse reaction leading to dose reduction was diarrhea (1.0%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Waldenström's Macroglobulinemia (WM)
The safety of BRUKINSA was evaluated in relapsed/refractory (RR) or treatment-naïve WM patients with *MYD88* mutation (*MYD88*^{MUT}) in a Phase 3, randomized, open-label clinical trial, BGB-3111-302, that included 101 patients treated with BRUKINSA at a dose of 160 mg twice daily and 98 patients treated with ibrutinib (Cohort 1). Additionally, 28 patients with RR or treatment-naïve WM found to have *MYD88* wildtype (*MYD88*^{WT}) (N=26) or missing/inconclusive *MYD88* status (N=2) were treated with BRUKINSA in a non-randomized exploratory arm (Cohort 2).

In Cohort 1, the median duration of treatment was 18.7 months in the BRUKINSA arm and 18.6 months in the ibrutinib arm. In Cohort 2, the median duration of treatment was 16.4 months.

Serious treatment-emergent adverse events occurred in 40% of patients in the BRUKINSA arm.

The most frequent serious adverse events were febrile neutropenia, influenza, and neutropenia (3% each); and anaemia, basal cell carcinoma, lower respiratory tract infection, pleural effusion, pyrexia, sepsis, and thrombocytopenia (2% each).

Of the 101 patients randomized and treated with BRUKINSA, 4% patients discontinued due to adverse events. The events leading to discontinuation were cardiomegaly, neutropenia, plasma cell myeloma, and subdural hemorrhage (1% each). Adverse events leading to dose reduction occurred in 14% of patients. The most common adverse events leading to dose reduction were neutropenia (3%) and diarrhea (2%).

Death due to adverse events within 30 days of last dose occurred in 1 (1%) patient. The adverse event leading to death was cardiomegaly.

Table 4 summarizes treatment-emergent adverse events in patients randomized in Cohort 1 in BGB-3111-302.

Table 4: Treatment-Emergent Adverse Events in ≥ 10% (All Grades*) of Patients with WM in BRUKINSA or Ibrutinib Arm of Cohort 1 in BGB-3111-302 Trial

System Organ Class Adverse Event	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or Higher (%)	All Grades* (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia	25	16	12	8
Anemia	12	5	10	5
Thrombocytopenia	10	6	10	3
Cardiac disorders				
Atrial fibrillation	2	0	14	3
Gastrointestinal disorders				
Diarrhea	21	3	32	1
Constipation	16	0	7	0
Nausea	15	0	13	1
Vomiting	9	0	13	1
General disorders and administration site conditions				
Fatigue	19	1	15	1
Pyrexia	13	2	12	2
Peripheral edema	9	0	19	0
Infections and infestations				

System Organ Class Adverse Event	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or Higher (%)	All Grades* (%)	Grade 3 or Higher (%)
Upper respiratory tract infection	24	0	29	1
Nasopharyngitis	11	0	7	0
Urinary tract infection	10	0	10	2
Pneumonia§	9	3	20	7
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain§	30	7	24	0
Pain in extremity	11	1	7	0
Muscle spasms	10	0	24	1
Nervous system disorders				
Headache	15	1	11	1
Dizziness	13	0	9	0
Renal and urinary disorders				
Hematuria	7	0	10	2
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14	0	6	0
Cough	13	0	17	0
Epistaxis	13	0	19	0
Skin and subcutaneous tissue disorders				
Rash§	18	0	21	0
Bruising§	18	0	34	0
Vascular disorders				
Hemorrhage§	21	5	24	4
Hypertension	11	6	16	11

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

§ Includes multiple preferred terms:

Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.

Hemorrhage includes all related terms containing hemorrhage, hematoma.

Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
Rash includes all related terms containing rash.

The safety profile of BRUKINSA in patients with WM in the non-randomized Cohort 2 (*MYD88*^{WT} or missing/inconclusive *MYD88* status, N = 28) was generally consistent with the safety profile for BRUKINSA in Cohort 1.

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment-emergent adverse events (regardless of causality) have been reported in the zanubrutinib arm of Cohort 1 of the BGB-3111-302 trial in more than 2 patients (adverse events addressed in Section 8.2 and laboratory abnormalities not included).

Blood and lymphatic system disorders: increased tendency to bruise

Cardiac disorders: palpitations, sinus bradycardia

Ear and labyrinth disorders: tinnitus

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain, angina bullosa haemorrhagica, dry mouth, dyspepsia, gastrooesophageal reflux disease, stomatitis

General disorders and administration site conditions: asthenia, chest pain, gait disturbance

Investigations: weight decreased

Metabolism and nutrition disorders: decreased appetite, dehydration

Musculoskeletal and connective tissue disorders: joint swelling, muscular weakness

Nervous system disorders: peripheral sensory neuropathy, syncope

Psychiatric disorders: depression

Renal and urinary disorders: nocturia, urinary retention

Respiratory, thoracic and mediastinal disorders: pleural effusion

Skin and subcutaneous tissue disorders: hyperhidrosis, petechiae, pruritus, purpura, skin lesion, skin ulcer

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematologic and Chemistry laboratory abnormalities are shown below.

Table 5: Laboratory Abnormalities* (>10%) in Patients with WM in Cohort 1 of BGB-3111-302 Trial

Laboratory Parameter	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or 4 (%)	All Grades* (%)	Grade 3 or 4 (%)
Hematologic laboratory abnormalities				
Hemoglobin decreased	18	5	17	6
Neutrophils decreased	48	22	32	6
Platelets decreased	34	7	38	5
Chemistry laboratory abnormalities				
Alanine aminotransferase increased	13	1	12	2
Aspartate aminotransferase increased	11	0	18	2
Bilirubin increased	11	1	31	1
Creatinine increased	31	1	19	0
Urate increased	14	3	32	3

* Based on laboratory measurements. Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

9 DRUG INTERACTIONS

9.1 Overview

Zanubrutinib is primarily metabolized by CYP3A. Concomitant use of BRUKINSA with medicinal products that strongly or moderately inhibit CYP3A can increase zanubrutinib plasma concentrations, which may increase the risk of BRUKINSA toxicities.

Concomitant use of BRUKINSA with moderate or strong CYP3A inducers can decrease zanubrutinib plasma concentrations, which may reduce BRUKINSA efficacy.

9.2 Drug-Drug Interactions

The drugs listed in Table 6 are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 6: Drug-Drug Interactions

Common Name	Source of Evidence	Effect	Clinical Comment
Active substances that may increase zanubrutinib plasma concentrations			
Strong CYP3A inhibitors (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	CT	Coadministration of itraconazole (200 mg once daily) increased zanubrutinib C_{max} by 157% and AUC by 278%.	Reduce BRUKINSA dosage to 80 mg once daily when co-administered with strong CYP3A inhibitors (see 4.2 Recommended Dose and Dosage Adjustment).
Moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant)	P	Coadministration of erythromycin (500 mg four time daily) was predicted to increase zanubrutinib C_{max} by 284% and AUC by 317%; Coadministration of fluconazole (200 mg once daily) was predicted to increase zanubrutinib C_{max} by 179% and AUC by 177%; Coadministration of fluconazole (400 mg once daily) was predicted to increase zanubrutinib C_{max} by 270% and AUC by 284%; Coadministration of diltiazem (200 mg once daily) was predicted to increase zanubrutinib C_{max} by 151% and AUC by 157%.	Reduce BRUKINSA dosage to 80 mg twice daily when co-administered with moderate CYP3A inhibitors (see 4.2 Recommended Dose and Dosage Adjustment).
Active substances that may decrease zanubrutinib plasma concentrations			
Strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin)	CT	Co-administration of rifampin (600 mg once a day for 8 days) decreased zanubrutinib C_{max} by 92% and AUC by 93%.	Avoid concomitant use of BRUKINSA with strong CYP3A inducers.
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	P	Co-administration of efavirenz (600 mg once a day) was predicted to decrease zanubrutinib C_{max} by 58% and AUC by 60%	Avoid concomitant use of BRUKINSA with moderate CYP3A inducers,

CT = Clinical Trial; P = Predicted

Clinical Studies

Effects of Gastric Acid Reducing Agents on zanubrutinib: No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

Effects of zanubrutinib on CYP3A Substrates: Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%.
Effects of zanubrutinib on CYP2C19 Substrates: Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%.

Effects of zanubrutinib on Other CYP Substrates: No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics or predicted with rosiglitazone (CYP2C8 substrate) pharmacokinetics when co-administered with zanubrutinib.

Effects of zanubrutinib on Transporter Systems: Co-administration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34% and AUC by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when co-administered with zanubrutinib.

In Vitro Studies

Effects of zanubrutinib on CYP2B6 Substrates: In vitro, zanubrutinib is a weak inducer of CYP2B6.

Effects of Transporters on zanubrutinib: In vitro, zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

9.3 Drug-Food Interactions

Avoid concomitant use with grapefruit, grapefruit juice and Seville oranges, as they contain inhibitors of CYP3A and may increase zanubrutinib plasma concentrations.

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

9.4 Drug-Herb Interactions

Avoid St. John’s wort which may unpredictably decrease zanubrutinib plasma concentrations.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Zanubrutinib is a small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.

In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

10.2 Pharmacodynamics

BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over 24 hours at a total daily dose of 320 mg BRUKINSA in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94% and 100% following the approved recommended dosage of 320 mg once daily or 160 mg twice daily respectively.

Cardiac electrophysiology

At the approved recommended doses (320 mg once daily or 160 mg twice daily), there were no clinically relevant effects on the QTc interval. In a thorough QT study in healthy subjects, a single dose of 160mg or 480 mg zanubrutinib did not prolong the QT interval to any clinically relevant extent. The maximum plasma exposure of zanubrutinib in this study was close to the maximum plasma exposure observed in patients following the recommended dose of 320 mg once daily.

The effect of BRUKINSA on the QTc interval above the therapeutic exposure has not been evaluated.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of zanubrutinib were studied in healthy subjects and patients with B-cell malignancies. Zanubrutinib maximum plasma concentration (C_{max}) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,099 (42%) ng·h/mL following a 160 mg twice daily dose and 1,917 (59%) ng·h/mL following a 320 mg once daily dose. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 299 (56%) ng/mL following a 160 mg twice daily dose and 533 (55%) ng/mL following a 320 mg once daily dose.

Absorption: The median T_{max} of zanubrutinib is 2 hours.

Food effect: No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution: The geometric mean (%CV) apparent steady-state volume of distribution of zanubrutinib during the terminal phase (V_z/F) was 522 L (71%) following a 160 mg twice daily dose. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Metabolism: *In vitro*, zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Elimination: The mean half-life (t½) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib was 128 (61%) L/h.
Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (less than 1% unchanged).

Special Populations and Conditions
Based on population PK analysis, age (19 to 90 years), sex, race (Caucasian, Asian, and others), and body weight (36 to 144 kg) did not have clinically meaningful effects on the PK of zanubrutinib.

Pediatrics: No pharmacokinetic studies were performed with zanubrutinib in patients under 18 years of age.

Hepatic Insufficiency: The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child-Pugh class A), by 21% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child-Pugh class A), by 43% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 194% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

Renal Insufficiency: Zanubrutinib undergoes minimal renal elimination. Based on population PK analysis, mild and moderate renal impairment (CrCl ≥ 30 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of zanubrutinib. Limited PK data is available in patients with severe renal impairment (CrCl < 30 mL/min) or in patients requiring dialysis.

11 STORAGE, STABILITY AND DISPOSAL

Store BRUKINSA at room temperature, between 15°C-30°C, in the original bottle.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

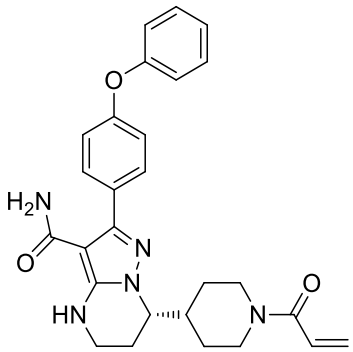
Drug Substance

Common name: zanubrutinib

Chemical name: ((7S)-2-(4-phenoxyphenyl)-7-[1-(prop-2-enoyl) piperidin-4-yl]-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrimidine-3-carboxamide)

Molecular formula and molecular mass: $C_{27}H_{29}N_5O_3$ and 471.55

Structural formula:



Physicochemical properties: Zanubrutinib is a crystalline white to off-white powder. The solubility of zanubrutinib is pH dependent, from very slightly soluble to practically insoluble in aqueous solutions.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Waldenström's Macroglobulinemia

The safety and efficacy of BRUKINSA were evaluated in a randomized, open-label, multi-center study comparing BRUKINSA and ibrutinib in 201 patients with MYD88 mutated (*MYD88*^{MUT}) WM (BGB-3111-302). In addition, a subset of WM patients found to have *MYD88* wildtype (*MYD88*^{WT}) by gene sequencing (N=26), or whose mutational status was missing or inconclusive (N=2), were enrolled in a third, non-randomized study arm (Table 7).

Table 7: Summary of Patient Demographics for Clinical Trials in Patients with WM

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
BGB-3111-302	(Cohort 1) Randomized (1:1), multi-center, open-label, Phase 3 Study	Arm A: BRUKINSA 160 mg orally twice daily	102	70 (range 45 to 87) years	M: 68% F: 32%
		Arm B: Ibrutinib 420 mg orally once daily	99	70 (range 38 to 90) years	M: 66% F: 34%
	(Cohort 2)	Arm C: BRUKINSA 160 mg orally twice daily	28	72 (range 39 to 87) years	M: 50% F: 50%
			Total N = 229		

Eligible patients were at least 18 years of age with a clinical and definite histological diagnosis of relapsed/refractory (RR) WM or treatment-naïve and considered to be unsuitable for standard chemo-immunotherapy regimens. Patients had to meet at least one criterion for treatment according to consensus panel criteria from the Seventh International Workshop on Waldenström's Macroglobulinemia (IWWM-7) and have measurable disease, as defined by a serum IgM level > 0.5 g/dl. Patients with *MYD88* mutation (*MYD88*^{MUT}) were assigned to Cohort 1 (N = 201) and were randomized 1:1 to receive either BRUKINSA 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Subjects found to have *MYD88* wildtype (*MYD88*^{WT}) by centrally confirmed gene sequencing (estimated to be present in approximately 10% of enrolled subjects), were enrolled to Cohort 2 (N = 26) and received BRUKINSA 160 mg twice daily on a third, non-randomized, study arm (Arm C). In addition, those subjects whose MYD88 mutational status was missing or inconclusive (N = 2) were assigned to Cohort 2, Arm C.

In Cohort 1, the median age was 70 years (range, 38 to 90 years), 28% were > 75 years (22% on the ibrutinib arm, 33% on the BRUKINSA arm), 67% were male, and 91% were Caucasian. At study entry, patients had an International Prognostic Scoring System (IPSS) high, derived using M-protein by serum protein electrophoresis (SPEP), as follows: 44% of patients in the ibrutinib arm and 46% of patients in the BRUKINSA arm. Ninety-four percent of patients had a baseline ECOG performance status of 0 or 1, and 6 % had a baseline ECOG performance status of 2. The median time from initial diagnosis was 4.6 years. Overall, 74 (37%) patients had IgM levels ≥ 40 g/L. One-hundred-sixty-four patients (82%) had RR WM. The median number of prior therapies was 1 (range, 1 to 8), and median time from initial diagnosis was 5.6 years. Patient disposition and demographics of patients with RR WM in Cohort 1 were generally similar between BRUKINSA and ibrutinib arms except pertaining to age. Compared with the ibrutinib

treatment arm, the BRUKINSA treatment arm had a higher proportion of patients ⩾ 75 years of age (32.5% versus 19.8%) and < 65 years of age (43.4% versus 32.1%).

In Cohort 2, the median age was 72 years (range, 39 to 87), 43% were > 75 years, 50% were male, and 96% were Caucasian. At study entry, 43% of the patients had an IPSS high (derived using M-protein by SPEP). Baseline ECOG performance status score was 0 or 1 in 86 % of patients and 14 % had a baseline ECOG performance status of 2. The median times from initial diagnosis was slightly shorter than in Cohort 1 (median 3.7 years versus 4.6 years).
Eight (29%) patients in Cohort 2 had IgM levels ≥ 40 g/L.Twenty-three of the 28 patients (82%) in Cohort 2 had RR disease, with a median number of prior therapies of 1 (range, 1 to 5).
Patient disposition and demographics of RR WM *MYD88*^{WT} patients were similar to those of RR WM *MYD88*^{MUT} patients in Cohort 1 except that RR WM *MYD88*^{WT} patients had a median of 4.0 years from initial diagnosis which was shorter than the median of 5.6 years for RR WM *MYD88*^{MUT} patients from Cohort 1.

The primary endpoint was rate of Complete Response (CR) or Very Good Partial Response (VGPR) in RR *MYD88*^{MUT} WM patients as assessed by Independent Review Committee (IRC) with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 included major response rate (MRR), duration of response, rate of CR or VGPR assessed by investigator, and progression-free survival (PFS).

14.2 Study Results

Waldenström's Macroglobulinemia

The primary efficacy analysis for patients with RR WM with *MYD88* mutation (*MYD88*^{MUT}), Cohort 1, was conducted at a median follow-up of 18.8 months in study BGB-3111-302 (ASPEN). As per IRC assessment, the primary study results failed to reach statistical significance in the RR Analysis Set (2-sided p = 0.12), thus the study did not meet the primary efficacy endpoint (Table 8). Consequently, all other endpoints are considered descriptive. Efficacy results, as assessed by Investigator, were consistent with the primary efficacy analysis.

Table 8: Efficacy Results Based on IRC in Patients with Waldenström's Macroglobulinemia (Study BGB-3111-302; Cohort 1)

Response Category	Treatment-naïve		Relapsed/Refractory		Overall (ITT)	
	BRUKINSA (N = 19)	Ibrutinib (N = 18)	BRUKINSA (N = 83)	Ibrutinib (N = 81)	BRUKINSA (N = 102)	Ibrutinib (N = 99)
Best Overall Response per IRC, %						
CR	0	0	0	0	0	0
VGPR	26	17	29	20	28	19
PR	47	50	49	61	49	59
MR	21	22	16	14	17	15
SD	0	6	4	3	3	3
PD	5	0	1	3	2	2

Response Category	Treatment-naïve		Relapsed/Refractory		Overall (ITT)	
	BRUKINSA (N = 19)	**Ibrutinib (N = 18)**	**BRUKINSA (N = 83)**	**Ibrutinib (N = 81)**	**BRUKINSA (N = 102)**	**Ibrutinib (N = 99)**
VGPR or CR Rate, n (%)	**5 (26.3)**	**3 (16.7)**	**24 (28.9)**	**16 (19.8)**	**29 (28.4)**	**19 (19.2)**
95% CI [c]	(9, 51)	(4, 41)	(20, 40)	(12, 30)	(20, 38)	(12, 28)
Risk difference, % [d]	-		10.7		10.2	
95% CI	(-, -)		(-3, 24)		(-2, 22)	
p-value [e]	-		**0.12**			

Abbreviations: CR, complete response; IRT, Interactive Response Technology; ITT, intent to treat; MR, minor response; MRR, major response rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on N.

[a] 95% CI is calculated using the Clopper-Pearson method.

[b] Mantel-Haenszel common risk difference with the 95% CI calculated using a normal approximation and Sato's standard error stratified by the stratification factors per IRT (strata CXCR4 WT and unknown are combined) and age group ($\leqslant$ 65 and > 65 years). Ibrutinib is the reference group.

[c] Based on Cochran-Mantel-Haenszel test stratified by the stratification factors per IRT (strata CXCR4 WT and unknown are combined) and age group ($\leqslant$ 65 and > 65 years). The p-value is 2-sided.

MRRs were 78% (95%CI: 68, 87) and 80% (95%CI: 70, 88) in the BRUKINSA and ibrutinib arms of the primary efficacy set (RR *WM MYD88^{MUT}* patients), respectively. MRRs for treatment naive patients were 74% (95% CI: 49, 91) and 67% (95% CI: 41, 87) in the BRUKINSA and the ibrutinib arms, respectively.

Median DoR of CR or VGPR and PFS were not reached in either arm of the primary efficacy set of RR *MYD88^{MUT}* WM patients.

In the non-randomized exploratory subset of BRUKINSA-treated *MYD88^{WT}* WM patients (Cohort 2), VGPR or CR rates as assessed by IRC were 20% (95% CI: 1, 72) for treatment-naïve patients (n=5) and 29% (95% CI: 11, 52), for RR patients (n=21). No CRs were observed.

15 MICROBIOLOGY

Not Applicable

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The general toxicologic profiles of zanubrutinib were characterized via oral treatment in Sprague-Dawley rats for up to 6 months and in Beagle dogs for up to 9 months.

In the 6-month study, rats were dosed 30, 100 or 300 mg/kg/day for 182 days, or 1000 mg/kg/day for up to 8 days. The test article related mortality was only noted at the dose of 1000 mg/kg/day following 5-day treatment and the main toxicology findings was gastrointestinal tract toxicity associated with histopathologic changes. Test article related histopathologic changes were noted in pancreas, lung, and skeletal muscle most of which were fully or partially

reversible. The NOAEL was considered to be 300 mg/kg/day, where the systemic exposure (AUC) was approximately 25 times in males and 42 times in females of the human exposure at the recommended dose.

In the 9-month study, dogs were dosed 10, 30 or 100 mg/kg/day for 273 days. No mortality occurred throughout the study. The toxicology findings or changes were minimal or mild and resolved during recovery phase, including abnormal stool, conjunctiva hyperemia, lymphoid depletion or erythrophagocytosis in the gut-associated lymphoid tissues. The NOAEL was considered to be 100 mg/kg/day, where the systemic exposure (AUC) was approximately 20 times in males and 18 times in females of the human exposure at the recommended dose.

Carcinogenicity

Carcinogenicity studies have not been conducted with zanubrutinib.

Genotoxicity

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in rats.

Developmental and Reproductive Toxicity

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating, and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the high dose of 300 mg/kg day, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 9 times the human recommended dose, based on body surface area.

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels (incidence between 0.3% to 1.5%) in the absence of maternal toxicity. The lowest dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 33 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study in rats, zanubrutinib was administered orally at 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the 75 mg/kg/day and 150 mg/kg/day groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately4 times the exposure (AUC) in patients receiving the recommended dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]BRUKINSA®
zanubrutinib capsules

Read this carefully before you start taking **BRUKINSA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BRUKINSA**.

Serious Warnings and Precautions

- Take BRUKINSA only under the care of a doctor who is experienced in the use of anti-cancer drugs.
- **Hemorrhage (serious or fatal bleeding problems)** may occur when you take BRUKINSA. This can be bleeding a lot, or bleeding that is difficult to stop. Your risk of bleeding is increased when taking BRUKINSA with blood thinner medications or other medications that prevent blood clots.

What is BRUKINSA used for?

BRUKINSA is used in adults to treat:

- Patients with a kind of cancer called Waldenström's Macroglobulinemia (WM**).**

How does BRUKINSA work?

BRUKINSA blocks a specific protein in the body that helps cancer cells live and grow. This protein is called "Bruton's Tyrosine Kinase." By blocking this protein, BRUKINSA may help kill and reduce the number of cancer cells and slow the spread of the cancer.

What are the ingredients in BRUKINSA?

Medicinal ingredients: zanubrutinib
Non-medicinal ingredients: ammonium hydroxide (trace), colloidal silicon dioxide, croscarmellose sodium, dehydrated ethanol (trace), gelatin, iron oxide black (trace), isopropyl alcohol (trace), magnesium stearate, microcrystalline cellulose, n-butyl alcohol (trace), propylene glycol (trace), purified water (trace), shellac glaze in ethanol (trace), sodium lauryl sulphate, titanium dioxide.

BRUKINSA comes in the following dosage forms:

Capsules: 80 mg

Do not use BRUKINSA if:

- You are allergic to zanubrutinib or any other ingredients in BRUKINSA. If you are not sure about this, talk to your doctor before taking BRUKINSA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BRUKINSA. Talk about any health conditions or problems you may have, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop treatment with BRUKINSA for 3 to 7 days before or after a surgery. This includes any planned medical, surgical, or dental procedure.

- have or had heart rhythm problems. Your risk for heart rhythm problems is increased if you have or had heart problems, high blood pressure or acute infections. Speak to your doctor immediately if you have ever experienced any of the following: fast and/or irregular heartbeat, dizziness, chest pain, shortness of breath, or if you faint. Your doctor may monitor the condition of your heart during your treatment with BRUKINSA.
- have or had liver problems.
- have severe kidney disease or are on dialysis.

Other warnings you should know about:

Treatment with BRUKINSA can increase your risk of certain side effects, including:
- **Interstitial lung disease:** Lung diseases that inflame or scar lung tissue.
- **New Cancers**: New cancers have happened in people during treatment with BRUKINSA. This includes cancers of the skin or other organs. Use sun protection when you are outside in sunlight.
- **Infections**: Serious and fatal infections have been reported in patients who are treated with BRUKINSA. Taking BRUKINSA may increase your risk of developing the following infections
    - Pneumonia. Pneumonia is an infection deep in the lungs.
    - Hepatitis B infection. Hepatitis B infection is a viral infection in the liver.
    - Shingles. Shingles is due to a virus that causes a painful skin rash.

Pregnancy, breastfeeding and fertility

Female patients
If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.
- Avoid becoming pregnant while you are taking BRUKINSA. It may harm or cause death of your unborn baby.
- If you are able to become pregnant, your doctor will do a pregnancy test before you start treatment with BRUKINSA.
- Effective birth control methods should be used during treatment with BRUKINSA. Talk to your doctor about birth control methods that may be right for you. You should use appropriate birth control methods for at least one week after your final dose of BRUKINSA.
- If you are breastfeeding or plan to breastfeed. It is not known if BRUKINSA passes into your breast milk. Do not breastfeed during treatment with BRUKINSA and for 2 weeks after your final dose of BRUKINSA. Talk to your doctor about the best way to feed your baby during this time.

Male Patients
- Use highly effective birth control while you are on BRUKINSA and for at least 3 months after your last dose if your partner can get pregnant.

Children and adolescents
BRUKINSA is not for use in patients under 18 years of age.

Driving and Using Machines: Before you do tasks that may require special attention, wait until you know how you respond to BRUKINSA. If you have blurred vision, feel tired or dizzy, do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BRUKINSA:
- Antibiotics used to treat bacterial infections (clarithromycin, erythromycin, rifampin).
- Medicines for fungal infections (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole).
- Medicines for HIV infection (indinavir, ritonavir).
- Medicines to treat low blood sodium levels (conivaptan).
- Medicines to treat hepatitis C (telaprevir).
- Medicines used to prevent seizures or to treat epilepsy or medicines used to treat a painful condition of the face called trigeminal neuralgia (carbamazepine, phenytoin).
- Medicines used to treat heart conditions or high blood pressure (diltiazem, verapamil).
- St. John's Wort.
- Grapefruit, grapefruit juice and Seville oranges.

How to take BRUKINSA:
- Take it exactly as your healthcare provider tells you. Do not decrease, stop or change your dose on your own.
- Take at about the same time each day.
- Take with or without food.
- Swallow whole with a glass of water. Do NOT chew, dissolve or open the capsule.

Usual Adult Dose:
Take 320 mg daily. Take two 80 mg capsules twice a day (twelve hours apart) OR four 80 mg capsules once a day.

Do not take BRUKINSA with the following:
- grapefruit, grapefruit juice and Seville oranges
- St. John's wort

Your doctor may change your usual dose depending on whether you experience side effects while taking BRUKINSA.

Overdose:

If you think you have taken too much BRUKINSA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as possible on the same day. Take your next dose of BRUKINSA at the normal schedule the following day. Do not take an extra dose to make up for a missed dose.

What are possible side effects from using BRUKINSA?
These are not all the possible side effects you may feel when taking BRUKINSA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- abdominal pain, joint pain, muscle pain/aches, pain in the arms and legs, back pain

- acid reflux disease
- blurred vision
- chest pain
- constipation
- decrease in weight and appetite
- depression
- dizziness
- dry mouth
- excessive sweating
- fainting
- fever
- headache
- mouth sores
- nausea or vomiting
- numbness, tingling, muscle weakness and pain
- rash or redness of the skin
- ringing, buzzing, clicking or hissing in the ears
- swelling of the joints, legs or hands
- tiny red or purple spots on the skin, bruising, itching
- tiredness
- waking up at night to urinate

BRUKINSA can cause abnormal blood test results. Your doctor may do blood tests before you start BRUKINSA and while you take it. Your doctor will decide when to perform blood tests and may change your treatment depending on the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
High blood pressure		√	
Infections (from bacteria, a virus or fungus): Cough, infection in your blood (sepsis), nose (sinus infection), sore throat, fatigue, fever, chills and flu-like symptoms.		√	
Anemia (low red blood cells): Being short of breath. Feeling very tired. Having pale skin. Fast heartbeat. Loss of energy, or weakness.		√	
Neutropenia (low white blood cells, neutrophils): Fever, or infection. Fatigue. Aches and pains. Flu-like symptoms.		√	
Thrombocytopenia (low blood platelets): Bruising or bleeding		√	

for longer than usual if you hurt yourself. Fatigue and weakness.			
Diarrhea: Increased number of bowel movements. Watery stool. Stomach pain and/or cramps.	√		
Urinary tract infection: Pain or burning when urinating, bloody or cloudy urine, foul smelling urine.		√	
Pneumonia, Bronchitis (infection in the lungs): Cough with or without mucus. Fever, chills.		√	
Hemorrhage (serious bleeding problems): Bleeding a lot or uncontrollably. Blood in your stool or urine. Long-lasting headache. Feeling dizzy or confused. Nose bleeds. Coughing up blood. Increased bruising.		√	
New cancers of skin and other types of cancer.		√	
COMMON			
Being short of breath		√	
Arrhythmia (heart rhythm problems): Racing or uncomfortable or irregular heartbeat. Flip-flop feeling, or pain in your chest. Feeling dizzy or confused.		√	
Pleural effusion (fluid around the lungs): chest pain, difficult or painful breathing, cough.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15 to 30°C in original bottle.

Keep out of reach and sight of children.

If you want more information about BRUKINSA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website beigene.com or by calling 1-877-828-5598.

This leaflet was prepared by BeiGene Switzerland GmbH.

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