▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
BRUKINSA (zanubrutinib)

1 NAME OF THE MEDICINE

zanubrutinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 80 mg zanubrutinib.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to off-white opaque hard capsule of 22 mm in length (size 0), marked with “ZANU 80” in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Waldenström’s Macroglobulinemia (WM)

BRUKINSA is indicated for the treatment of adult patients with Waldenström’s macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Mantle cell lymphoma (MCL)

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication was approved via the **provisional approval** pathway, based on objective response rate. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Dose Modification for Adverse Reactions

Recommended dose modifications of zanubrutinib for Grade 3 or greater adverse reactions are provided in Table 1:

Table 1: Recommended Dose Modification for Adverse Reaction

Event	**Adverse Reaction Occurrence**	**Dose Modification (Starting Dose: 320 mg once daily or 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 zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

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

Missed Dose

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.

Method of administration

Zanubrutinib capsules should be administered orally as 320 mg once daily or 160 mg twice daily approximately every twelve hours. Zanubrutinib can be taken with or without food. Patients should be instructed to swallow capsules whole with water, and not to open, break or chew the capsules.

Special populations

Use in Children

The safety and efficacy of zanubrutinib have not been established in pediatric patients.

Use in the Elderly

No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

Patients with Renal Insufficiency

No dosage modification is recommended in patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for zanubrutinib adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis (see section 5.2 *Pharmacokinetic properties*).

Patients with Hepatic Insufficiency

Dose modifications are not needed in patients with mild or moderate hepatic impairment. Patients with mild or moderate hepatic impairment were treated in zanubrutinib clinical studies. The

recommended dose of zanubrutinib for patients with severe hepatic impairment is 80 mg orally twice daily. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse reactions of zanubrutinib (see section 5.2 *Pharmacokinetic properties*).

Interactions Requiring Dose Adjustments

Dose Modification for use with CYP3A inhibitors or inducers:

Table 2: Recommended Dose Modifications *[see 4.5 Interactions with other medicines and other forms of interactions and 5.2 Pharmacokinetic properties]*:

CYP3A	Co-administered Drug	Recommended Dose
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily Interrupt dose as recommended for adverse reactions *[see Dose and method of administration (4.2)]*.
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily Modify dose as recommended for adverse reactions *[see Dose and method of administration (4.2)]*.
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) and moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use; Consider alternative agents.

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

4.3 CONTRAINDICATIONS

None

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious and fatal haemorrhagic events have occurred in patients with haematological malignancies treated with zanubrutinib monotherapy. Grade 3 or higher bleeding events occurred in 4.1% of patients, including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported uncommonly in patients. Bleeding events of any grade occurred in 55.8% of patients with haematological malignancies, including purpura and petechiae.

Zanubrutinib may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding zanubrutinib for 3-7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred in patients with haematological malignancies treated with zanubrutinib monotherapy. Grade 3 or higher infections

occurred in these patients. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) or herpes zoster virus reactivation have occurred.

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

Effects on Laboratory Tests - Cytopenias

Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements were reported in patients with haematologic malignancies treated with zanubrutinib monotherapy (see Section 4.8 *Adverse effects (Undesirable effects)*.

Monitor complete blood counts during treatment. See Section 4.2 *Dose and method of administration* for recommended dose modifications.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma of any grade have occurred in 14.1% of patients with haematological malignancies treated with zanubrutinib monotherapy. The most frequent second primary malignancy was skin cancer (9.2%) (basal cell carcinoma [5.1%] and squamous cell carcinoma of skin [3.3%]). Second primary malignancies of Grade 3 or higher have occurred in 5.6% of patients. Advise patients to use sun protection.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter of any grade have occurred in 3.2% of patients with haematological malignancies treated with zanubrutinib monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 or higher events occurred in 1.0% of patients. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Paediatric use

The safety and efficacy of BRUKINSA in children below 18 years of age have not been established.

Use in the elderly

No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of Other Drugs on BRUKINSA

Table 3: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Pharmacokinetic Properties (5.2)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Posology and Method of Administration (4.2)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Pharmacokinetic Properties (5.2)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Posology and Method of Administration (4.2)]*.

Drug Interaction Studies

Agents that may increase zanubrutinib plasma concentrations

CYP3A Inhibitors: The coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the C_{max} of zanubrutinib by 2.6-fold and AUC by 3.8-fold. Physiologically based PK (PBPK) simulations indicate that coadministration of multiple doses of a moderate CYP3A inhibitor (e.g. fluconazole, diltiazem and erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold.

Concomitant use of zanubrutinib and medicinal products that strongly or moderately inhibit CYP3A can increase zanubrutinib exposure.

Agents that may decrease zanubrutinib plasma concentrations

CYP3A Inducers: Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92 % and AUC by 93%. PBPK simulations indicate that a moderate CYP3A inducer (e.g. efavirenz) may decrease zanubrutinib Cmax by 58% and AUC by 60%.

Concomitant use of zanubrutinib and strong or moderate inducers of CYP3A can decrease zanubrutinib plasma concentrations.

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

Agents that may have their plasma concentrations altered by zanubrutinib

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

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

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.

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

CYP Enzymes: Zanubrutinib is a weak inducer of CYP2B6.

Transporter Systems: Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effect on male or female fertility was noted in rats but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 19 and 32 times the human recommended dose in male and female rats, respectively, based on AUC.

Use in pregnancy – Category D

Women will be advised to avoid pregnancy and breastfeeding infants while taking zanubrutinib. If zanubrutinib is used during pregnancy or if the patient becomes pregnant while taking zanubrutinib, the patient should be apprised of the potential hazard to the fetus.

Women should avoid becoming pregnant while taking zanubrutinib and for at least one week after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking zanubrutinib and for at least one week after stopping treatment. Pregnancy testing is recommended for females of reproductive potential prior to initiating zanubrutinib therapy. Men should be advised to avoid fathering a child while receiving zanubrutinib and for at least 1 week following the last dose of zanubrutinib.

Malformations in the heart (2- or 3-chambered hearts) were observed in rats given zanubrutinib at all oral doses of 30, 75 or 150 mg/kg/day during organogenesis, in the absence of maternotoxicty. The lowest dose of 30 mg/kg/day is approximately 4 times the human recommended dose, based on AUC.

Embryotoxicity (post-implantation loss) was observed in rabbits given zanubrutinib during the period of organogenesis at doses of 150 mg/kg/day and was associated with maternotoxicity. The dose of 150 mg/kg/day is approximately 25 times the human recommended dose, based on AUC.

Use in lactation

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from zanubrutinib in a breastfed child, advise lactating women not to breastfeed during treatment with zanubrutinib and for at least two weeks following the last dose.

In a pre- and postnatal developmental toxicity study, zanubrutinib was administered to rats at doses of 30, 75, and 150 mg/kg from implantation through weaning. At doses from 75 mg/kg/day, offspring had decreased body weights pre-weaning. All dose groups had offspring with increased incidences of adverse ocular findings (e.g. cataract, protruding eye). The significance of which is unclear. The dose of 30 mg/kg/day is approximately 4 times the human recommended dose, based on AUC.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile is based on pooled data from 779 patients with B-cell malignancies treated with zanubrutinib in 6 clinical trials with a median duration of treatment of 30.3 months, including one Phase 1 clinical study (BGB-3111-1002), one Phase 1/2 clinical study (BGB-3111-AU-003), three Phase 2 studies (BGB-3111-205, BGB-3111-206, BGB-3111-210), and one Phase 3 clinical study (BGB-3111-302).

The most commonly occurring adverse reactions in the 6 studies combined (≥ 20%) were neutropenia[†], thrombocytopenia[†], upper respiratory tract infection[§], haemorrhage/haematoma[§], rash[§], bruising[§], anaemia[†], musculoskeletal pain, diarrhea, pneumonia[§] and cough. The most common Grade 3 or higher adverse reactions (≥ 5%) were neutropenia, thrombocytopenia, pneumonia, and anemia.

Discontinuation and dose reduction

Of the 779 patients treated with zanubrutinib, 28 (3.6%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia[§] (1.8%). Adverse reactions leading to dose reduction occurred in 4.9% of patients.

Presented in Table 4 below are adverse reactions that have been reported in association with the use of zanubrutinib monotherapy in the 6 clinical studies. Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

Table 4: Adverse Reactions in Patients Treated with Zanubrutinib

MedDRA SOC	Group Terms/PTs	Zanubrutinib N=779	
		All Grades*(%)	Grade≥3 (%)
Infections and infestations	Upper respiratory tract infection§	Very Common (44.3)	2.6
	Pneumonia§ #	Very Common (22.1)	11.6
	Pneumonia	Very Common (16.3)	10.1
	Lower respiratory tract infection	Common (6.2)	0.8
	Urinary tract infection	Very Common (15.5)	2.3
	Hepatitis B reactivation	Common (1.2)	0.8
Blood and lymphatic system disorders	Neutropenia†	Very Common (56.2)	28.0
	Thrombocytopenia†	Very Common (45.1)	11.4
	Anaemia†	Very Common (28.9)	6.9
Nervous system disorder	Dizziness§	Very Common (11.7)	0.4
Vascular disorders	Bruising§	Very Common (29.1)	0.1
	Contusion	Very Common (21.1)	0.0
	Petechiae	Common (5.6)	0.0
	Ecchymosis	Common (2.3)	0.1
	Haemorrhage/Haematoma§ #	Very Common (32.2)	3.1
	Haematuria	Very common (14.5)	0.6
	Epistaxis	Common (8.5)	0.1
	Gastrointestinal haemorrhage	Uncommon (0.5)	0.3
Gastrointestinal disorders	Diarrhea	Very Common (23.6)	1.8
	Constipation	Very Common (15.0)	0.4

Skin and subcutaneous tissue disorders	Rash[§]	Very Common (29.8)	0.4
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[§]	Very Common (24.3)	2.4
	Back pain	Very Common (11.7)	1.0
	Arthralgia	Very Common (10.9)	1.0
General disorders and administration site conditions	Fatigue[§]	Very common (19.8)	1.5
	Fatigue	Very common (15.3)	1.2
	Asthenia	Common (3.6)	0.3
Respiratory, thoracic and mediastinal disorders	Cough	Very Common (21.7)	0.1

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

[†] Based on laboratory measurements.

[§] Includes multiple adverse reaction terms.

Includes events with fatal outcome

Hemorrhage: Serious and fatal hemorrhagic events have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Infections: Cases of fatal and non-fatal infections have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Cytopenias: Cases of neutropenia, anemia and thrombocytopenia have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Second primary malignancies: Cases of second primary malignancies have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Atrial fibrillation and flutter: Cases of atrial fibrillation and flutter have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

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, randomised, 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-randomised exploratory arm (Cohort 2).

In Cohort 1, the median duration of treatment was 30.3 months in the BRUKINSA arm and 29.9 months in the ibrutinib arm. In Cohort 2, the median duration of treatment was 27.8 months.

Serious treatment-emergent adverse events occurred in 48.5% of patients in the BRUKINSA arm. The most frequent serious adverse events were febrile neutropenia, influenza, pyrexia, and neutropenia

(3% each); and anaemia, pneumonia, basal cell carcinoma, lower respiratory tract infection, pleural effusion, sepsis, and thrombocytopenia (2% each).

Of the 101 patients randomised and treated with BRUKINSA, 5% patients discontinued due to adverse events. The events leading to discontinuation were cardiomegaly, neutropenia, plasma cell myeloma, drug-induced liver injury and subdural hemorrhage (1% each). Adverse events leading to dose reduction occurred in 14.9% 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 5 summarises treatment emergent adverse events in patients randomised in Cohort 1 in BGB-3111-302.

Table 5: Treatment-Emergent Adverse Events in ≥ 10% (All Grades*) of Patients with WM in Zanubrutinib 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	26.7	18.8	14.3	9.2
Anemia	12.9	5.9	15.3	6.1
Thrombocytopenia	12.9	6.9	12.2	5.1
Cardiac disorders				
Atrial fibrillation	5.0	0	17.3	6.1
Palpitation	5.0	0	10.2	0
Gastrointestinal disorders				
Diarrhea	21.8	3	33.7	2.0
Nausea	17.8	0	15.3	1.0
Constipation	16.8	0	7.1	0
Vomiting	12.9	0	15.3	1.0
General disorders and administration site conditions				
Fatigue	24.8	1.0	19.4	1.0
Pyrexia	15.8	4.0	13.3	2.0
Peripheral edema	13.9	0	20.4	0
Infections and infestations				
Upper respiratory tract infection	30.9	0	31.6	1.0
Pneumonia§	12.9	4	24.5	10.2
Nasopharyngitis	10.9	0	7.1	0
Urinary tract infection	10.9	0	15.3	2.0

System Organ Class Adverse Event	**BRUKINSA (N = 101)**		**Ibrutinib (N = 98)**	
	All Grades* (%)	**Grade 3 or Higher (%)**	**All Grades* (%)**	**Grade 3 or Higher (%)**
Localised infection	1.0	0	11.2	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain§	36.3	7.9	32.7	1.0
Pain in extremity	13.9	1.0	8.2	0
Muscle spasms	9.9	0	27.6	1.0
Nervous system disorders				
Headache	17.8	1.0	14.3	1.0
Dizziness	13.9	1.0	12.2	0
Renal and urinary disorders				
Hematuria	9.9	1.0	12.2	2.0
Respiratory, thoracic and mediastinal disorders				
Cough	16.8	0	19.4	0
Epistaxis	15.8	1.0	20.4	0
Dyspnea	14.9	0	7.1	0
Injury, poisoning and procedural complications				
Contusion	14.9	0	25.5	0
Skin and subcutaneous tissue disorders				
Bruising§	19.8	0	33.7	0
Rash§	19.8	0	23.5	0
Pruritus	12.9	1.0	6.1	0
Vascular disorders				
Hemorrhage§	24.8	5.0	27.6	5.1
Hypertension	13.9	8.9	21.4	15.3

* 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 viral, pneumonia aspiration, lower respiratory tract infection.
Rash includes all related terms containing rash

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

Hematologic and Chemistry laboratory abnormalities are shown below.

Table 6: 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 (%)
Haematologic laboratory abnormalities				
Haemoglobin decreased	20.8	6.9	22.4	9.2
Neutrophils decreased	52.0	25.0	36.1	9.3
Platelets decreased	35.6	8.9	39.8	5.1
Chemistry laboratory abnormalities				
Alanine aminotransferase increased	15.8	2.0	14.4	2.1
Aspartate aminotransferase increased	12.0	1.0	18.9	2.1
Bilirubin increased	13.0	2.0	33.0	1.0
Creatinine increased	30.7	1.0	23.5	1.0
Urate increased	17.0	3.2	35.6	5.6

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

Mantle Cell Lymphoma (MCL)

The safety of zanubrutinib was evaluated in 118 patients with MCL who received at least one prior therapy at a dose of 320 mg daily in two single-arm clinical trials, BGB-3111-206 and BGB-3111-AU-003. The median duration of treatment was 22.8 months.

Serious treatment-emergent adverse events occurred in 33.9% of patients. The most frequent (≥ 2% of patients) serious adverse events were lung infection (6.8%), pneumonia (4.2%), and anaemia (2.5%).

Of the 118 MCL patients treated with zanubrutinib, 13.6% patients discontinued treatment due to adverse events. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%; grouped terms). Adverse events leading to dose reduction occurred in 3.4% of patients; these included hepatitis B, neutropenia, allergic dermatitis, and peripheral sensory neuropathy (in 1 patient each).

Death due to adverse events within 30 days of last dose occurred in 9 (7.6%) patients. The adverse events leading to death were road traffic accident, cerebral hemorrhage, cerebral infarction, congestive cardiac failure, pneumonia (in 2 patients; grouped terms) and unknown reason (in 3 patients).

Table 7 summarises treatment emergent adverse events in BGB-3111-206 and BGB-3111-AU-003.

Table 7: Treatment-Emergent Adverse Events in ≥ 10% (All Grades*) of Patients With Previously Treated MCL in BGB-3111-206 and BGB-3111-AU-003 Trials

System Organ Class Adverse Event	**BRUKINSA (N = 118)**	
	All Grades* (%)	**Grade 3 or Higher (%)**
Blood and lymphatic system disorders		
Neutrophil count decreased and neutropenia	38	15
Platelet count decreased and thrombocytopenia	31	7
White blood cell count decreased and leukopenia	26	6
Anemia and hemoglobin decreased	15	8
Gastrointestinal disorders		
Diarrhea	23	1
Constipation	14	1
Infections and infestations		
Upper respiratory tract infection§	37	0
Pneumonia§	17	12
Urinary tract infection	13	1
Investigations		
Alanine aminotransferase increased	12	1
Metabolism and nutrition disorders		
Hypokalemia	14	2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain§	14	3
Respiratory, thoracic and mediastinal disorders		
Cough	14	0
Skin and subcutaneous tissue disorders		
Rash§	37	0
Bruising§	14	0
Vascular disorders		
Hemorrhage§	12	3
Hypertension	11	3

* 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.
Upper respiratory tract infection includes PTs of upper respiratory tract infection and viral upper respiratory tract infection.

Hematologic and Chemistry laboratory abnormalities are shown below.

Table 8: Selected Laboratory Abnormalities*(>10%) in Patients With MCL in BGB-3111-206 and BGB-3111-AU-003 Trials

Laboratory Parameter	BRUKINSA (N = 101)	
	All Grades* (%)	Grade 3 or 4 (%)
Hematologic laboratory abnormalities		
Neutrophils decreased	45	20
Platelets decreased	44	9
Hemoglobin decreased	30	6
Lymphocytes increased	41	16
Chemistry laboratory abnormalities		
Alanine aminotransferase increased	30	1
Bilirubin increased	26	1
Urate increased	31	3

* Based on laboratory measurements (at least 1 severity grade higher than at baseline). Grades w ere evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCA E) version 4.03.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, Bruton’s tyrosine kinase inhibitors. ATC code: L01EL03.

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 signalling

molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling 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 tumour growth.

Pharmacodynamic effects

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 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.

Effect on QT/QTc interval and 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. At a single dose 1.5 times the maximum recommended dose (480 mg), zanubrutinib did not prolong the QT interval to any clinically relevant extent (i.e., ≥10 msec).

Clinical trials

Waldenström's Macroglobulinemia (WM)

BGB-3111-302: A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton tyrosine kinase Inhibitors BGB-3111 and Ibrutinib in Patients with Waldenström Macroglobulinemia

BGB-3111-302 is a randomised, open-label, multicentre study comparing zanubrutinib and ibrutinib in subjects with Waldenström macroglobulinemia (WM). Eligible patients were at least 18 years of age with a clinical and definite histological diagnosis of relapsed/refractory WM or treatment-naïve when considered by their treating physician 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) 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 randomised 1:1 to receive either zanubrutinib 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 gene sequencing (estimated to be present in approximately 10% of enrolled subjects), were enrolled to Cohort 2 (N = 26) and received zanubrutinib 160 mg twice daily on a third, non-randomised, 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 overall, the median age was 70 years (range, 38 to 90 years), 27.9% were > 75 years (22.2% on the ibrutinib arm, 33.3% on the zanubrutinib arm), 67 % were male, and 91% were Caucasian. At study entry, patients had an International Prognostic Scoring System (IPSS) high categorisation, derived using M-protein by serum protein electrophoresis (SPEP), as follows: 44.4% of patients in the ibrutinib arm and 46.1% of patients in the zanubrutinib arm. Ninety-four percent of patients had a baseline ECOG performance status of 0 or 1, and 6.5% had a baseline ECOG

performance status of 2. One-hundred-sixty-four patients had relapsed or refractory disease; the median number of prior therapies was 1 (range, 1 to 8). The median time from initial diagnosis was 4.63 years. Overall, 74 (37 %) patients had IgM levels ≥ 40 g/L.

In Cohort 2, the median age was 72 years (range, 39 to 87), 42.9% were > 75years, 50% were male, and 96.4 % were Caucasian. At study entry, 42.9% of the patients had an IPSS high categorisation (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. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease, with a median number of prior therapies of 1 (range, 1 to 5). The median times from initial diagnosis was slightly shorter than in Cohort 1 (median 3.65 years versus 4.6 years). Eight (29 %) patients in Cohort 2 had IgM levels ≥ 40 g/L.

In Cohort 1, the primary outcome measure was rate of Complete Response (CR) or Very Good Partial Response (VGPR), as assessed by IRC with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 include MRR, duration of response, rate of CR or VGPR determined by investigator, PFS, resolution of treatment-precipitating symptoms, and anti-lymphoma effects. The median follow-up was 19.4 months (range 0.5 to 31.1 months) for ibrutinib - treated patients and 19.5 months (range 0.4 to 31.2 months) for zanubrutinib-treated patients. The study did not meet statistical significance for the pre-specified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN. Results are shown in Table 9.

Table 9: Analysis of Disease Response Per Overall Combined Assessment by Independent Review Committee (Study BGB-3111-302; Cohort 1) (Overall WM Population)

Response Category	**Ibrutinib N = 99**	**Zanubrutinib N = 102**
VGPR or CR rate, n (%)	**19 (19.2)**	**29 (28.4)**
95% CI [a]	(12.0, 28.3)	(19.9, 38.2)
Risk difference (%) [b]	10.2	
95% CI [a]	(-1.5, 22.0)	
p-value [c]	**0.0921**	
MRR (PR or better), n (%)	**77 (77.8)**	**79 (77.5)**
95% CI [a]	(68.3, 85.5)	(68.1, 85.1)
Risk difference (%) [b]	-0.5	
95% CI	(-12.2, 11.1)	
ORR (MR or better), n (%)	**92 (92.9)**	**96 (94.1)**
95% CI [a]	(86.0, 97.1)	(87.6, 97.8)

Percentages are based on N.
[a] 2-sided Clopper-Pearson 95% confidence interval.
[b] Mantel-Haenszel common risk difference with the 95% confidence interval calculated using a normal approximation and Sato's standard error stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65). Ibrutinib is the reference group.
[c] Based on CMH test stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65)

In the overall population in Cohort 1, the event-free rates at 12 months for patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 87.2% versus 89.7%, respectively, and 83.8% versus 85.0% at 18 months. The event-free rates at 12 months for relapsed/refractory

patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 85.9% versus 92.4%, respectively, and 81.7% versus 85.9% at 18 months.

Results for Cohort 2 are presented in Table 10.

Table 10: Analysis of Disease Response Per Overall Combined Assessment by Independent Review Committee (Study BGB-3111-302; Cohort 2) (Efficacy Analysis Set)

Response Category	**Zanubrutinib N = 26**
VGPR or CR rate, n (%)	**7 (26.9)**
95% CI [a]	(11.6, 47.8)
MRR (PR or better), n (%)	**13 (50.0)**
95% CI [a]	(29.9, 70.1)
ORR (MR or better), n (%)	**21 (80.8)**
95% CI [a]	(60.6, 93.4)

Percentages are based on N.
[a] Includes patients whose only overall tumor response available is progressive disease unconfirmed (PDu).

In the overall population in Cohort 2, the event-free rates at 12 and 18 months were 72.4% and 68.1%, respectively, per overall combined assessment.

BGB-3111-AU-003: A Phase I/II, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB 3111 in Patients With B-Cell Lymphoid Malignancies

BGB-3111-AU-003 is a Phase 1/2 open-label, dose-escalation, multicentre, single arm trial of B-cell malignancies including 78 WM patients. Zanubrutinib was given orally at starting doses ranging from 40 mg daily to 160 mg twice daily until disease progression or unacceptable toxicity. Most patients (93%) received a total daily dose of 320 mg daily (either 320 mg once daily or 160 mg twice daily).

The median age of patients was 67 years (range 40 to 87), 80% were male, and 86 % were Caucasian. Ninety-six percent of patients had a baseline ECOG performance status of 0 or 1, and 4 % had a baseline ECOG performance status of 2. Fifty-four patients had relapsed or refractory disease; the median number of prior therapies was 2 (range, 1 to 8). The median time from initial diagnosis was 4.31 years. Overall, 24 (31%) patients had IgM levels ≥ 40 g/L.

Seventy-three patients were evaluable for efficacy. Assessment of response was evaluated using the combined response criteria updated at the Sixth IWWM. Results by investigator are shown in Table 11.

Table 11: Assessment of Response (WM Efficacy Evaluable Set) Per Overall Combined Assessment by Investigator (BGB-3111-AU-003)

Response Category	Relapsed/Refractory WM (N = 49)	Total WM (N = 73)
Best Overall Response, n (%)		
CR	1 (2.0)	1 (1.4)
VGPR	24 (49.0)	32 (43.8)
PR	14 (28.6)	27 (37.0)
VGPR or CR Rate, n (%)	25 (51.0)	33 (45.2)
95% CI [a]	(36.3, 65.6)	(33.5, 57.3)
Major Response Rate (PR or Better), n (%)	39 (79.6)	60 (82.2)
95% CI [a]	(65.7, 89.8)	(71.5, 90.2)
Overall Response Rate (MR or Better), n (%)	46 (93.9)	70 (95.9)
95% CI [a]	(83.1, 98.7)	(88.5, 99.1)
Median Study Follow-up (Range)	35.81 (4.44, 57.17)	30.32 (4.44, 57.17)

Abbreviations: BTK, Bruton tyrosine kinase; CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response, R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström's macroglobulinemia
Percentages are based on N, the number of patients in the WM Efficacy Evaluable Set (i.e., received ≥ 1 dose of zanubrutinib, had baseline IgM or M-protein ≥ 5 g/L, and no prior exposure to a BTK inhibitor).
[a] Calculated using the Clopper-Pearson method.
Data cut-off 31 August 2019

The median durations of VGPR or CR, major response, and overall response have not been reached for the total WM population or relapsed/refractory patients who achieved a response to study treatment.

The estimated event-free rates at 12, 18, and 24 months for the total WM patient population who achieved a major response were 91.6%, 88.0%, and 83.2%, respectively.

Mantle Cell Lymphoma (MCL)

BGB-3111-206: A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

BGB-3111-206 is a Phase 2 open-label, multicentre, single arm trial of 86 previously treated MCL patients. Zanubrutinib was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.

The median age of patients was 60.5 years (range 34 to 75) and the majority were male (77.9%). The median time since diagnosis was 30 months and the median number of prior therapies was 2 (range 1 to 4). The most common prior regimens were CHOP-based (90.7%) followed by rituximab-based (74.4%). The majority of patients had extranodal involvement (70.9%) and refractory disease

(52.3%). Blastoid variant of MCL was present in 14% of patients. The combined biologic MIPI score (which includes age, ECOG score, baseline lactate dehydrogenase, WBC count and Ki-67% staining in tumor cells) was intermediate in 45.3% and high risk in 38.4%.

Tumor response was according to the 2014 Lugano Classification and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee (IRC).

Table 12: BGB-3111-206 Efficacy Results in MCL Patients by Independent Review Committee

	Study BGB-3111-206 (N=86)
Median Follow Up Time	18.4 months
ORR (95% CI)	83.7% (74.2, 90.8)
CR	68.6%
PR	15.1%
Median DoR in months (95% CI)	19.5 (16.6, NE)

Note: Percentages were based on N.
ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: non-evaluable.

BGB-3111-AU-003: A Phase I/II, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB 3111 in Patients With B-Cell Lymphoid Malignancies

BGB-3111-AU-003 is a Phase 1/2 open-label, dose-escalation, multicentre, single arm trial of B-cell malignancies including 37 previously treated MCL patients. Zanubrutinib was given orally at starting doses ranging from 40 mg daily to 160 mg twice daily until disease progression or unacceptable toxicity. Most patients (32/37) received a total daily dose of 320 mg daily (either 320 mg once daily or 160 mg twice daily).

The median age of patients of the 32 R/R MCL patients receiving 320 mg daily was 70 years (range 42 to 86), and 37.5% of patients were ≥75 years old. The majority of patients were male (68.8%). The median time since diagnosis was 4.5 years and the median number of prior therapies was 1 (range 1 to 4). The most common prior regimens were rituximab-based (93.8%) followed by CHOP-based regimen (59.4%). The majority of patients had extranodal involvement (78.1%), and 25% had refractory disease. The MIPI score (which includes age, ECOG score, baseline lactate dehydrogenase and WBC count) was intermediate in 40.6% and high risk in 31.3%.

Tumor response was according to the 2014 Lugano Classification and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee. PET scans were not required per protocol, and most responses were assessed using CT imaging.

Table 13: BGB-3111-AU-003 Efficacy Results in MCL Patients by Independent Review Committee

	Study BGB-3111-AU-003 (N=32)
Median Follow Up Time	14.75 months
ORR (95% CI)	84.4% (67.2, 94.7)
CR	25.0%*
PR	59.4%
Median DoR in months (95% CI)	18.53 (12.58, NE)

Note: Percentages were based on N.
ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, PFS: progression free survival, CI: confidence interval, NE: non-evaluable.
* Only CT scans were mandated.

5.2 PHARMACOKINETIC PROPERTIES

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. 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 (Vz/F) was 522 (71%) L. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio was 0.7-0.8.

Metabolism

Zanubrutinib is primarily metabolised by cytochrome P450(CYP)3A. None of these metabolites are considered to contribute significantly to the safety and efficacy profile of zanubrutinib.

Excretion

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 during the terminal phase was 128 (61%) L/h.

Following a single radiolabelled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in faeces (38% unchanged) and 8% in urine (less than 1% unchanged).

Special Populations

Age

Age (19 to 90 years) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Gender

Gender had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Race

Ethnicity (Asian, Caucasian, and Other) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Body Weight

Body weight (36 to 140 kg) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

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.

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.

5.3 PRECLINICAL SAFETY DATA

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 at oral doses up to 2000 mg/kg.

Carcinogenicity

Carcinogenicity studies have not been conducted with zanubrutinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content
Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Colloidal anhydrous silica
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide

Printable ink
OPACODE monogramming ink S-1-277002 BLACK

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in Original Container.

6.5 NATURE AND CONTENTS OF CONTAINER

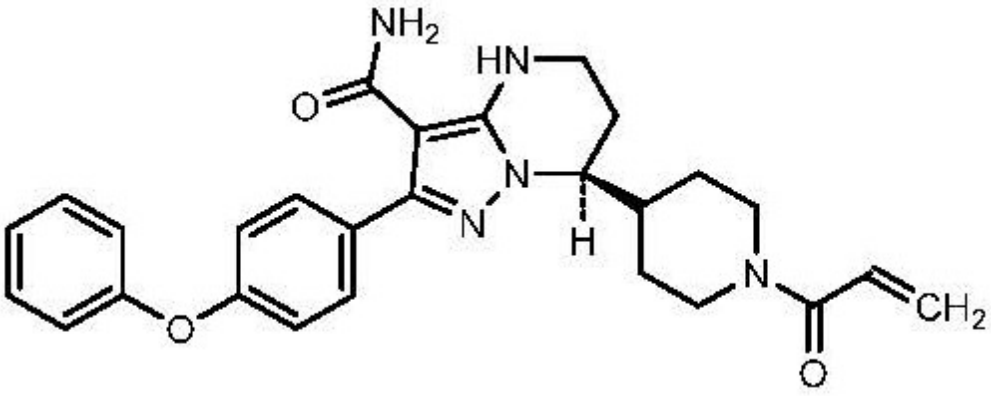
HDPE bottles with a child-resistant polypropylene closure. Each carton contains one bottle. Each bottle contains 120 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1691249-45-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

BeiGene AUS Pty Ltd
1C/528 Compton Road
Stretton
Queensland 4116
Australia

9 DATE OF FIRST APPROVAL

07 October 2021

10 DATE OF REVISION

08 October 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Added new indication – MCL
4.8	Added safety information for MCL indication
5.1	Added clinical efficacy data for MCL