ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

BRUKINSA 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 80 mg of zanubrutinib.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRUKINSA as monotherapy 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.

BRUKINSA as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.

BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended total daily dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules). Treatment with Brukinsa should be continued until disease progression or unacceptable toxicity.

Dose modifications for adverse reactions

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

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction	**Adverse reaction occurrence**	**Dose modification (starting dose: 320 mg once daily or 160 mg twice daily)**
≥Grade 3 non-haematological toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting > 10 consecutive days) Grad 4 thrombocytopenia (lasting >10 consecutive days)	First	Interrupt BRUKINSA Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt BRUKINSA Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice 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 BRUKINSA.

Dose modifications for concomitant therapy

Dose modifications for use with CYP3A inhibitors or inducers (see sections 4.4, 4.5 and 5.2):

Table 2: Recommended dose modifications when co-administered with other medicinal products

CYP3A	**co-administered medicinal product**	**recommended dose**
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) Moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use; Consider alternative agents with less CYP3A induction

Missed dose

A double dose should not be taken to make up for a forgotten dose. If a dose is not taken at the scheduled time, the next dose should be taken according to the normal schedule.

Special populations

Elderly

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

Renal impairment

No dose modification is recommended in patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min, estimated by Cockcroft-Gault). There is limited data on patients with severe renal impairment and end-stage renal disease (n=12). Patients with severe renal impairment (CrCl <30 mL/min) or on dialysis should be monitored for adverse reactions (see section 5.2).

Hepatic impairment

Dose modifications are not needed in patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). Patients with mild or moderate hepatic impairment were treated in BRUKINSA clinical studies. The recommended dose of BRUKINSA for patients with severe hepatic impairment (Child-Pugh class C) is 80 mg orally twice daily. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse events of BRUKINSA (see section 5.2).

Paediatric population

The safety and efficacy of BRUKINSA in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

BRUKINSA is for oral use. The hard capsules can be taken with or without food. Patients should be instructed to swallow the capsules whole with water, and not to open, break or chew the capsules.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Serious and fatal haemorrhagic events have occurred in patients treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported in patients (see section 4.8). Bleeding events of any grade including purpura and petechiae occurred in patients with haematological malignancies. The mechanism for the bleeding events is not well understood.

BRUKINSA may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Dose modification may be necessary for Grade 3 or greater adverse reactions as recommended (see section 4.2). Warfarin or other vitamin K antagonists should not be administered concomitantly with BRUKINSA. Patients should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with BRUKINSA.

Infections

Fatal and non-fatal infections (including bacterial, viral, fungal infections, or sepsis) and opportunistic infections (e.g. herpes viral, cryptococcal, aspergillus and pneumocystis jiroveci infections) have occurred in patients treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in patients (see section 4.8). The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have also occurred. Before initiating treatment with BRUKINSA, patients' HBV status should be established. Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. Patients should be monitored and managed according to the medical standards to prevent hepatitis B reactivation. Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Patients should be monitored for signs and symptoms of infection and treat appropriately.

Cytopenia

Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements were reported in patients treated with BRUKINSA monotherapy (see section 4.8). Monitor complete blood counts monthly during treatment (see section 4.2).

Second primary malignancies

Second primary malignancies, including non-skin carcinoma have occurred in patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin). Advise patients to use sun protection.

Atrial fibrillation and flutter

Atrial fibrillation and atrial flutter have occurred in patients treated with BRUKINSA monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Tumour Lysis Syndrome

Tumour lysis syndrome has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for chronic lymphocytic leukaemia (CLL) Assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Women of childbearing potential

Women of childbearing potential must use a highly effective method of contraception while taking Brukinsa (see section 4.6).

BRUKINSA contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

Zanubrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A).

Agents that may increase zanubrutinib plasma concentrations

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

Strong 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 in healthy subjects.

If a strong CYP3A inhibitor must be used (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir), reduce the BRUKINSA dose to 80 mg (one capsule) for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see section 4.2).

Moderate CYP3A inhibitors

Physiologically based pharmacokinetics simulations indicate that coadministration of multiple doses of a moderate CYP3A inhibitor may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. If a moderate CYP3A inhibitor must be used (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges), reduce the BRUKINSA dose to 160 mg (two capsules) for the duration of the inhibitor use. Monitor patients closely for toxicity and follow dose modification guidance as needed (see section 4.2).

Mild CYP3A inhibitors

Simulations using fasted conditions suggested that the mild CYP3A inhibitors (e.g., cyclosporine and fluvoxamine) may increase the AUC of zanubrutinib by <1.5-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patients closely for toxicity and follow dose modification guidance as needed.

Grapefruit and Seville oranges should be used with caution during BRUKINSA treatment, as these contain moderate inhibitors of CYP3A (see section 4.2).

Agents that may decrease zanubrutinib plasma concentrations

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

CYP3A inducers

Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased zanubrutinib C_{max} by 92% and AUC by 93% in healthy subjects. Concomitant use with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided (see section 4.2). Co-administration of multiple doses of rifabutin (moderate CYP3A inducer) decreased zanubrutinib C_{max} by 48% and AUC by 44% in healthy subjects. Mild CYP3A inducers may be used with caution during BRUKINSA treatment.

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

Zanubrutinib is a mild inducer of CYP3A and CYP2C19. Concomitant use of zanubrutinib can decrease the plasma concentrations of these substrate medicinal products.

CYP3A substrates

Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%. Narrow therapeutic index medicinal products that are metabolised by CYP3A (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be used with caution, as zanubrutinib may decrease the plasma exposures of these medicinal products.

CYP2C19 substrates

Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%. Narrow therapeutic index medicinal products that are metabolized by CYP2C19 (e.g., S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these medicinal products.

Other CYP substrates

No clinically significant differences were observed with S-warfarin (CYP2C9 substrate) pharmacokinetics when co-administered with zanubrutinib.

Co-administration with transport substrates/inhibitors

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.

The coadministration of oral P-gp substrates with a narrow therapeutic index (e.g., digoxin) should be done with caution as zanubrutinib may increase their concentrations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Based on findings in animals, BRUKINSA may cause foetal harm when administered to pregnant women (see section 5.3). Women should avoid becoming pregnant while taking BRUKINSA and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking BRUKINSA and for up to 1 month after stopping treatment. It is currently unknown whether zanubrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. Pregnancy testing is recommended for women of reproductive potential prior to initiating therapy.

Pregnancy

BRUKINSA should not be used during pregnancy. There are no data from the use of BRUKINSA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

It is not known whether zanubrutinib or its metabolites are excreted in human milk and no non-clinical studies were conducted. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Brukinsa.

Fertility

No effect on male or female fertility was noted in rats but morphological abnormalities in sperm and increased post-implantation loss were noted at 300 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

Brukinsa has no or negligible influence in the ability to drive and use machines. 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 Undesirable effects

Summary of the safety profile

The most commonly occurring adverse reactions (≥20%) were upper respiratory tract infection[§] (33%), bruising[§] (30%), neutropenia[§] (28%), haemorrhage/haematoma[§] (27%), rash[§] (23%), and musculoskeletal pain[§] (23%) (Table 3).

The most common Grade 3 or higher adverse reactions (>5%) were neutropenia[§] (19%), pneumonia[§] (9%), hypertension (7%), and thrombocytopenia[§] (6%).

Of the 1550 patients treated with zanubrutinib, 2.9% of patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia[§] (1.4%). Adverse reaction leading to dose reduction occurred in 5.7% of patients.

Tabulated list of adverse reactions

The safety profile is based on pooled data from 1550 patients with B-cell malignancies, including patients with chronic lymphocytic leukaemia (N = 938), Waldenström macroglobulinemia (N = 249), mantle cell lymphoma (N = 140), marginal zone lymphoma (N = 93), follicular lymphoma (N = 59) and other types of B-cell malignancies (N = 71), treated with BRUKINSA in clinical studies with a median duration of exposure of 22.95 months.

Adverse reactions in patients treated with BRUKINSA for B-cell malignancies are listed below by system organ class and frequency grouping. Frequencies are defined as follows: 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 the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions reported in clinical studies in patients with B-cell malignancies

MedDRA SOC	MedDRA Terms	All Grades* (%)	Grade 3 or higher (%)
Infections and infestations	Upper respiratory tract infection[§]	Very Common (33)	2
	Pneumonia[§#]	Very Common (18)	9

	Pneumonia	Very Common (12)	7
	Lower respiratory tract infection	Common (5)	<1
	Urinary tract infection	Very Common (12)	2
	Bronchitis	Common (4)	<1
	Hepatitis B reactivation	Uncommon (<1)	<1
Blood and lymphatic system disorders	Neutropenia[§]	Very Common (28)	19
	Febrile neutropenia	Common (1)	1
	Thrombocytopenia[§]	Very Common (16)	6
	Anaemia[§]	Very Common (14)	5
Nervous system disorder	Dizziness[§]	Very Common (11)	<1
Cardiac disorders	Atrial fibrillation and flutter	Common (3)	1
Vascular disorders	Bruising[§]	Very Common (30)	<1
	Contusion	Very Common (18)	0
	Petechiae	Common (7)	<1
	Purpura	Common (5)	<1
	Ecchymosis	Common (2)	<1
	Haemorrhage/Haematoma[§ #]	Very Common (27)	3
	Haematuria	Very common (10)	<1
	Epistaxis	Common (7)	<1
	Gastrointestinal haemorrhage	Uncommon (<1)	<1
	Hypertension[§]	Very Common (13)	7
Respiratory, thoracic and mediastinal disorders	Cough	Very Common (19)	<1
Gastrointestinal disorders	Diarrhoea	Very Common (19)	2
	Constipation	Very Common (12)	<1
Skin and subcutaneous tissue disorders	Rash[§]	Very Common (23)	<1
	Pruritus	Common (7)	<1
	Dermatitis exfoliative general	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[§]	Very Common (23)	2
	Arthralgia	Very Common (13)	<1
	Back pain	Very common (10)	<1
General disorders and administration site conditions	Fatigue[§]	Very common (16)	1
	Fatigue	Very common (12)	1
	Asthenia	Common (4)	<1
	Oedema peripheral	Common (7)	<1
Metabolism and nutrition disorders	Tumour lysis syndrome[§#]	Uncommon (<1)	<1

Investigations[†]	Absolute neutrophil count decreased[†±]	Very common (49)	21
	Platelets decreased[†±]	Very common (36)	7
	Haemoglobin decreased[†±]	Very common (23)	4

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.
[†] Based on laboratory measurements.
[±] Percentages are based on number of patients with both baseline and at least one postbaseline assessment available.
[§] Includes multiple adverse reaction terms
Includes events with fatal outcome.

Other special population

Elderly

Of the 1550 patients treated with BRUKINSA, 61.3% were 65 years of age or older. The incidence of Grade 3 or higher adverse events was slightly higher among elderly patients treated with zanubrutinib (60.3% of patients age ≥65 versus 54.0% of patients <65 years of age). No clinically relevant differences in safety were observed between patients ≥65 years and younger.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Zanubrutinib is an inhibitor of Bruton's tyrosine kinase (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.

Pharmacodynamic effects

BTK occupancy in PBMCs 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% to 100% following the recommended dose.

Effect on QT/QTc interval and cardiac electrophysiology

At the 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 efficacy and safety

Patients with Waldenström Macroglobulinemia (WM)
The safety and efficacy of BRUKINSA in WM were evaluated in a randomized, open-label, multicentre study comparing zanubrutinib and ibrutinib (ASPEN study) in patients who were BTK inhibitor naive. 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 unsuitable for standard chemo-immunotherapy regimens by their treating physician. 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 randomized 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 = 28) and received zanubrutinib 160 mg twice daily on a third, non-randomized, study arm (Arm C).

In Cohort 1 ($MYD88^{MUT}$), the median age was 70 years (range, 38 to 90 years), with 71% and 60% of patients treated with ibrutinib and zanubrutinib respectively being >65 years old. 33% of patients in the zanubrutinib arm and 22% in the ibrutinib were >75 years. 67% were male, and 91% were Caucasian. At study entry, 44% of patients in the ibrutinib arm and 46% of patients in the zanubrutinib arm had an International Prognostic Scoring System (IPSS) high. One hundred and sixty-four patients had relapsed or refractory disease; the median number of prior therapies was 1 (range, 1 to 8).

The primary outcome measure was rate of Complete Response (CR) or Very Good Partial Response (VGPR), as assessed by an independent review committee (IRC) with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 include major response rate (MRR), duration of response, rate of CR or VGPR determined by investigator, and progression-free survival (PFS).

The testing for the superiority of the primary endpoint of VGPR or CR rate required testing in the Relapsed/Refractory Analysis Set prior to testing in the ITT Analysis Set. Median follow-up was 19.4 months. In the relapsed/refractory patients, 19.8% and 28.9% achieved VGPR or CR on the ibrutinib and zanubrutinib arms, respectively. The primary efficacy endpoint was not significant in the Relapsed/Refractory Analysis Set (2-sided p=0.1160). Table 4 summarizes the responses as assessed by IRC for the Relapsed/Refractory and intent-to-treat (ITT) Analysis Set. Responses were observed with zanubrutinib across subgroups, including $MYD88^{WT}$ patients (Cohort 2) who had a VGPR or CR rate of 26.9% and an MRR of 50%.

Table 4: Primary analysis of disease response by independent review committee (ASPEN Study)

	Relapsed/Refractory		ITT	
Response Category	**Ibrutinib N = 81**	**Zanubrutinib N = 83**	**Ibrutinib N = 99**	**Zanubrutinib N = 102**
Median follow-up time, months (range)	18.79 (0.5, 30.0)	18.73 (0.4, 28.7)	19.38 (0.5, 31.1)	19.47 (0.4, 31.2)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VGPR	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)
PR	49 (60.5)	41 (49.4)	58 (58.6)	50 (49.0)
VGPR or CR rate, n (%)	**16 (19.8)**	**24 (28.9)**	19 (19.2)	29 (28.4)
95% CI [a]	(11.7, 30.1)	(19.5, 39.9)	(12.0, 28.3)	(19.9, 38.2)
Risk difference (%) [b]	10.7		10.2	
95% CI [a]	(-2.5, 23.9)		(-1.5, 22.0)	
p-value [c]	**0.1160**			
MRR (PR or better), n (%)	65 (80.2)	65 (78.3)	77 (77.8)	79 (77.5)
95% CI [a]	(69.9, 88.3)	(67.9, 86.6)	(68.3, 85.5)	(68.1, 85.1)
Risk difference (%) [b]	-3.5		-0.5	
95% CI	(-16.0, 9.0)		(-12.2, 11.1)	
Duration of major response				
Event-free rate at, % (95% CI)[d] 18 months	85.6 (73.1, 92.6)	87.0 (72.5, 94.1)	87.9 (77.0, 93.8)	85.2 (71.7, 92.6)

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)

[d] Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Based on an updated data cut-off the progression free-survival event-free rate by investigator assessment was 77.6% vs 84.9% at 30 months (ibrutinib vs zanubrutinib), with an estimated overall hazard ratio of 0.734 (95% CI: 0.380, 1.415).

Patients with Marginal Zone Lymphoma (MZL)

The efficacy of zanubrutinib was assessed in a Phase 2 open-label, multicentre, single-arm trial of 68 patients with MZL who had received at least one prior anti-CD20-based therapy. Twenty-six (38.2%) patients had extranodal MZL, 26 (38.2%) had nodal MZL, 12 (17.6%) had splenic MZL, and in 4 (6%) patients, the subtype was unknown. Zanubrutinib was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity. The median age of patients was 70 years (range: 37 to 95), and 53% were male. The median time since initial diagnosis was 61.5 months (range: 2.0 to 353.6). The median number of prior treatments was 2 (range: 1 to 6), with 27.9 % patients having 3 or more lines of systemic therapy; 98.5% (n=67) patients had received prior rituximab-based chemotherapy and 85.3% (n=58) patients had received prior treatment with alkylating agents; 5.9% patients (n=4) had prior stem cell transplantation. Sixty-three (92.6%) patients had a baseline ECOG performance status of 0 or 1. Twenty-two (32.4%) patients had refractory disease at study entry.

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 5: Efficacy Results in Patients with MZL by Independent Review Committee Error! No document variable supplied.

	Study BGB-3111-214 (N=66) [a]
ORR (95% CI)	68% (55.6,79.1)
CR	26%
PR	42%
Median DoR in months (95% CI)	NE (25.0, NE)
DOR Event Free Rate [b] at 24 months, % (95% CI)	72.9 (54.4, 84.9)
Median study follow-up in months (Min, Max)	28.04 (1.64, 32.89)

a Two patients in BGB-3111-214 were not evaluable for efficacy due to central confirmation of MZL transformation to diffuse large B-cell lymphoma.
b Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable

In BGB-3111-214, the median time to response was 2.79 months (range: 1.7 to 11.1 months). After a median study follow-up time of 28.04 months (range: 1.64 to 32.89 months), the median duration of response (DOR) as assessed by the IRC has not been reached (95% CI 25.0 months to NE), and a total of 72.9 % (95% CI 54.4 to 84.9) of responders were estimated to be event-free at 24 months after initial response.

The overall response rates observed were similar across three different MZL subtypes (extranodal, nodal and splenic).

Patients with Chronic Lymphocytic Leukaemia (CLL)

The efficacy of BRUKINSA in patients with CLL was evaluated in two randomized controlled trials.

BGB-3111-304: An International, Phase 3, Open-label, Randomized Study of Zanubrutinib Compared with Bendamustine plus Rituximab (BR) in Patients with Previously Untreated CLL.

BGB-3111-304 is a randomized multicenter, open-label, active controlled Phase 3 trial of zanubrutinib monotherapy and bendamustine in combination with rituximab in 479 patients with previously untreated CLL without 17p deletion (del(17p)) (arms A and B; Cohort 1). BGB-3111-304 arm C (Cohort 2) is a multicenter single-arm trial of zanubrutinib monotherapy in 110 patients with previously untreated CLL with centrally confirmed del(17p).

Both Cohorts enrolled patients 65 years of age or older as well as patients between 18 and 65 years of age that were unsuitable for chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR).

Demographic and baseline characteristics were generally balanced between arm A (zanubrutinib) and arm B (BR) of Cohort 1. In both arms, the median age was 70.0 years, with a slightly higher proportion of patients of ≥ 75 years (26.1%) in arm A compared with arm B (22.3%) and a slightly lower proportion of patients 65-75 years old (55.2%) in arm A compared with arm B (58.4%). In Cohort 1, 92.7% patients had a baseline ECOG performance status of 0 or 1 (93.7% in arm A and 91.6% in arm B). In Cohort 2 (arm C zanubrutinib), 87.3% patients had a baseline ECOG performance status of 0 or 1.

Demographic and baseline characteristics were also generally similar between arm A (zanubrutinib) in Cohort 1 and arm C (zanubrutinib) in Cohort 2.

In Cohort 1, randomisation was stratified by age (< 65 years vs ≥ 65 years), Binet stage (C versus A or B), immunoglobulin variable region heavy chain (IGHV) mutational status (mutated vs unmutated), and geographic region (North America versus Europe versus Asia Pacific). A total of 479 patients were randomized (intent-to-treat [ITT] analysis set), 241 to zanubrutinib continuous monotherapy and 238 to 6 cycles of therapy with bendamustine and rituximab (BR).

In Cohort 1, patients in the zanubrutinib arm A received 160 mg twice daily until disease progression or unacceptable toxicity. In arm B, patients received bendamustine at a dose of 90 mg/m2/day on the first 2 days of each cycle for 6 cycles and rituximab at a dose of 375 mg/m2 for Cycle 1, and at a dose of 500 mg/m2 for Cycles 2 to 6. Each treatment cycle consisted of approximately 28 days. In Cohort 2 (arm C), patients received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity.

For Cohort 1, the primary endpoint was progression-free survival (PFS), assessed by an independent central review committee (IRC). Secondary endpoints included the overall response rate based on IRC assessment.

In Cohort 1, the median duration of follow-up for PFS was 25.0 months (range: 0.0 to 41.4). The PFS rate at 24 months was 85.5% (95% CI: 80.1, 89.6) for zanubrutinib and 69.5% (95% CI: 62.4, 75.5) for BR. In Cohort 2, the median duration of follow up for PFS was 27.9 months (range: 1.0 to 38.8) and the PFS rate at 24 months 88.9% (95% CI: 81.3, 93.6). The ORR assessed by IRC in Cohort 2 was 90.0% (95% CI: 82.8, 94.9). The median time to partial response or higher as assessed by IRC was 2.89 months (range: 1.8, 14.2) and 2.86 months (range: 1.9, 13.9) in the zanubrutinib arm of Cohort 1 and Cohort 2, respectively.

Efficacy results for cohort 1 is presented in Table 66. The Kaplan-Meier curves for PFS for both arms in Cohort 1 are shown in Figure 1.

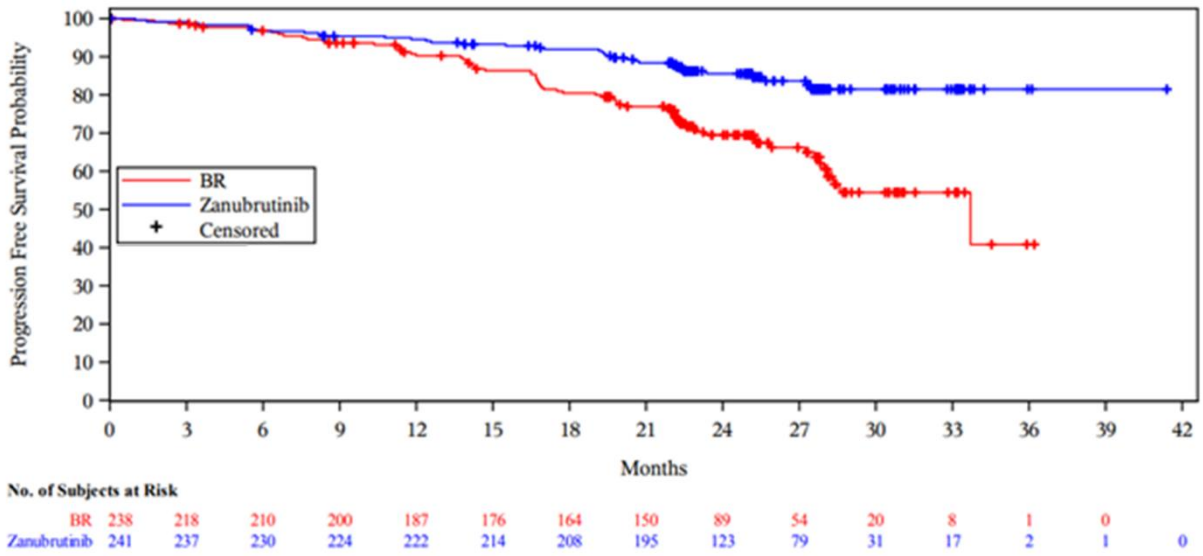
Table 6: Efficacy Results in BGB-3111-304

	Cohort 1* Patients without Del(17p)		~~**Cohort 2** Patients with Del(17p)~~
Endpoint	**Zanubrutinib** **(N=241)**	**Bendamustine + Rituximab** **(N=238)**	~~**Zanubrutinib** **(N=110)**~~
Progression-Free Survival†			
Number of Events, n (%)	36 (14.9)	71 (29.8)	~~15 (13.6)~~
Disease Progression, n (%)	27 (11.2)	59 (24.8)	~~14 (12.7)~~
Death, n (%)	9 (3.7)	12 (5.0)	~~1 (0.9)~~
Median (95% CI), months [a]	NE (NE, NE)	33.7 (28.1, NE)	~~NE (NE, NE)~~
Hazard Ratio (95% CI) [b]	0.42 (0.28, 0.63)		~~N/A~~
P value [c]	<0.0001		~~N/A~~
Overall Response Rate† % (95% CI)	94.6% (91.0, 97.1)	85.3% (80.1, 89.5)	~~90.0% (82.8, 94.9)~~

Overall Response Rate: CR+CRi+nPR+PR+PR-L, CR: complete response, CRi: complete response with incomplete haematopoietic recovery, nPR: nodular partial response, PR: partial response, PR-L: partial response with lymphocytoma, CI: confidence interval, NE: not estimable, median follow-up time for PFS was 25.0 months (95% CI: 24.6, 25.2).
* ITT analysis set
† Assessed by independent central review committee.
a Based on Kaplan-Meier estimation.
b Based on a stratified Cox-regression model with bendamustine + rituximab as the reference group.
c Based on a stratified log-rank test.

At an updated ad hoc analysis with a median follow-up of 33.5 months for PFS, the investigator-assessed PFS remained consistent with the primary analysis with a HR of 0.33 (95% CI: 0.22 to 0.48, descriptive P<0.0001) in the zanubrutinib arm over the BR arm. Median PFS was not reached with zanubrutinib arm and was 39.2 months for BR arm. At 36 months after randomization, 83.6% of patients treated with zanubrutinib and 55.1% with BR were estimated to be progression-free and alive. With a median follow-up of 35.8 months, the median OS was not reached for both arms; the 36-month OS rate estimate was 90.9% (95% CI: 86.3 to 94.0) in the zanubrutinib arm and 89.5% (95% CI: 84.2 to 93,1) in the BR arm, respectively.

Figure 1: Kaplan-Meier Curve of IRC-assessed PFS in BGB-3111-304 Cohort 1 (ITT population)



BGB-3111-305: A Phase 3, Randomized Study of Zanubrutinib Compared with Ibrutinib in Patients with Relapsed/Refractory (R/R) CLL

BGB-3111-305 is a randomized, multicenter, open-label, Phase 3, active controlled trial. It enrolled 652 patients with relapsed or refractory CLL after at least one prior systemic therapy. The patients were randomized to either zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily, continued until disease progression or unacceptable toxicity.

Randomization was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/*TP53* mutation status (present or absent).

Baseline demographics and disease characteristics were generally balanced between treatment arms in ITT analysis set and in the first 415 randomized patients.

In the ITT analysis set, the median age was 67.0 years in the zanubrutinib arm and 68.0 years in the ibrutinib arm. The majority of patients in both arms had an ECOG PS of 0 or 1 (97.9% in the zanubrutinib arm; 96.0% in the ibrutinib arm). Similar demographics and baseline characteristics were observed in the first 415 randomized patients. The median number of prior lines of systemic therapy is 1.0 the zanubrutinib arm (range, 1 to 6) and 1.0 in the ibrutinib arm (range, 1 to 8) in both the ITT analysis set and the first 415 randomized patients.

Patients previously treated with a BTK inhibitor were excluded from study 305 and limited data for zanubrutinib after prior BCL 2 inhibitor treatment is available.

Of 652 patients total, 327 were assigned to zanubrutinib monotherapy, 325 to ibrutinib monotherapy. The efficacy evaluation is based on the pre-specified interim analysis of the first 415 randomized patients of the ITT population. Of these, 207 were randomized to zanubrutinib monotherapy, 208 to ibrutinib monotherapy. Efficacy results are presented in Table 7.

The primary endpoint was overall response rate (ORR, defined as partial response or better).

At the pre-specified ORR interim analysis in the first 415 randomised patients, zanubrutinib demonstrated non-inferiority (1-sided p <0.0001) and superiority (2-sided p = 0.0006) to ibrutinib in the protocol-specified primary endpoint ORR assessed by investigator. Response as determined by IRC also demonstrated non-inferiority of zanubrutinib to ibrutinib (1-sided p < 0.0001). At the ORR final analysis, ORR assessed by the investigator continues to be higher (79.5% versus 71.1%) in the zanubrutinib arm compared with the ibrutinib arm (descriptive p = 0.0133); ORR determined by IRC was also significantly higher in the zanubrutinib arm compared with the ibrutinib arm, demonstrating superiority (80.4% versus 72.9%, respectively; 2-sided p = 0.0264).

Table 7 Efficacy Results in BGB-3111-305 (Pre-specified Interim Analysis of the First 415 randomized Patients) by Investigator (protocol defined primary endpoint) and IRC Assessment

	Investigator Assessed (protocol-define primary endpoint)		**IRC Assessed**	
Endpoint	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**
Overall Response Rate[§] n (%) (95% CI)	162 (78.3) (72.0, 83.7)	130 (62.5) (55.5, 69.1)	158 (76.3) (69.9, 81.9)	134 (64.4) (57.5, 70.9)
Response ratio [a] (95% CI)	1.25 (1.10, 1.41)		1.17 (1.04, 1.33)	
Non-inferiority [b]	1-sided p-value <0.0001		1-sided p-value <0.0001	
Superiority [c]	2-sided p-value 0.0006		2-sided p-value 0.0121	
Duration of Response [d]: 12-months event-free rate % (95% CI)	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)	90.3 (82.3, 94.8)	78.0 (66.1, 86.2)

Overall Response Rate : CR + CRi + nPR + PR, CR: complete response, CRi: complete response with incomplete haematopoietic recovery, nPR: nodular partial response, PR: partial response, CI: confidence interval

Median duration of response as assessed by investigator was not reached in the zanubrutinib arm at interim analysis, median study follow-up time was 15.31 months (range: 0.1, 23.1) in zanubrutinib arm and 15.43 months (range: 0.1, 26.0) in ibrutinib arm.

[§] Hypothesis testing for the noninferiority of ORR at the interim analysis is based on the first 415 randomized patients only with a 1-sided significance level of 0.005.

[a] Response ratio: estimated ratio of the overall response rate in the zanubrutinib arm divided by that in the ibrutinib arm.

[b] Stratified test against a null response ratio of 0.8558.
[c] Stratified Cochran-Mantel-Haenszel test.
[d] Kaplan-Meier estimate.

The median time to response as assessed by the investigator at the ORR interim analysis in first 415 randomised patients was 5.59 months (range: 2.7, 14.1) in zanubrutinib arm and 5.65 months (range: 2.8, 16.7) in ibrutinib arm. The results assessed by IRC were consistent (5.55 months vs. 5.63 months in zanubrutinib and ibrutinib arms respectively). At the ORR final analysis in all 652 randomised patients, the median time to response remained unchanged (5.59 months vs. 5.65 months as assessed by investigator and 5.52 months vs. 5.62 months as assessed by IRC in zanubrutinib and ibrutinib arms respectively).

In patients with del(17p) mutation in the first 415 randomized patients, the ORR assessed by investigator were 83.3% (95% CI 62.5, 95.3; 20 of 24 patients) in the zanubrutinib arm and 53.8% (95% CI 33.4, 73.4; 14 of 26 patients) in the ibrutinib arm. Based on IRC assessment, the ORR were 79.2% (95% CI 57.8, 92.9; 19 of 24 patients) in the zanubrutinib arm and 61.5% (95% CI 40.6, 79.8; 16 of 26 patients) in the ibrutinib arm ~~group~~. At the ORR final analysis in all 652 randomized patients, the ORR assessed by investigator were 86.7% (95% CI 73.2, 94.9; 39 of 45 patients with del(17p) mutation) in the zanubrutinib arm and 56.0% (95% CI 41.3, 70.0; 28 of 50 patients with del(17p) mutation) in the ibrutinib arm. Based on IRC assessment, the ORR were 86.7% (95% CI 73.2, 94.9; 39 of 45 patients with del(17p) mutation) in the zanubrutinib arm and 64.0% (95% CI 49.2, 77.1; 32 of 50 patients with del(17p) mutation) in the ibrutinib arm.

For PFS in the total of 652 enrolled patients, at the time of ORR interim analysis the 12-month event-free rates assessed by investigator were 93.3% (95% CI, 89.3, 95.9) for the zanubrutinib arm and 83.1% (95% CI, 77.3, 87.6) for the ibrutinib arm; the 12-month event-free rates assessed by IRC were 90.4% (95% CI, 85.7, 93.6) for the zanubrutinib arm and 81.7% (95% CI, 75.8, 86.4) for the ibrutinib arm. With a median study follow-up time of 24.3 months (range: 0.1, 34.1) in zanubrutinib arm and 23.8 months (range: 0.1, 37.0) in ibrutinib arm at the ORR final analysis, the 24-month event-free rates assessed by investigator were 78.4% (95% CI, 72.3, 83.4) for the zanubrutinib arm and 63.6% (95% CI, 56.5, 69.8) for the ibrutinib arm, and the 24-month event-free rates assessed by IRC were 77.4% (95% CI, 71.2, 82.4) for the zanubrutinib arm and 65.8 % (95% CI, 58.9, 71.9) for the ibrutinib arm.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with BRUKINSA in all subsets of the paediatric population for the treatment of lymphoplasmacytic lymphoma and for the treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

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 dose 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 for one week.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,099 (42%) ng h/mL following 160 mg twice daily and 1,917 (59%) ng h/mL following 320 mg once daily. The geometric mean

(%CV) zanubrutinib steady-state C_{max} is 299 (56%) ng/mL following 160 mg twice daily and 533 (55%) ng/mL following 320 mg once daily.

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

Metabolism

Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Elimination

The mean half-life ($t_{½}$) 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

Elderly

Age (19 to 90 years; mean age 65±12.5) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=1291).

Paediatric population

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

Gender

Gender (872 males and 419 females) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Race

Race (964 White, 237 Asian, 30 Black, and 25 categorized as Other) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Body weight

Body weight (36 to 149 kg, mean weight 76.5±16.9 kg) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=1291).

Renal impairment

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. The analysis was based on 362 patients with normal renal function, 523 with mild renal impairment, 303 with moderate renal impairment, 11 with severe renal impairment, and one with ESRD. The effects of severe renal impairment (CrCl <30 mL/min) and dialysis on zanubrutinib pharmacokinetics is unknown.

Hepatic impairment

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. A significant correlation was observed between the Child-Pugh score, baseline serum albumin, baseline serum bilirubin and baseline prothrombin time with unbound zanubrutinib AUC.

In vitro studies

CYP enzymes

Zanubrutinib is a weak inducer of CYP2B6 and CYP2C8. Zanubrutinib is not an inducer of CYP1A2.

Co-administration with transport substrates/inhibitors

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

Pharmacodynamic interactions

An i*n vitro* study showed that the potential pharmacodynamic interaction between zanubrutinib and rituximab is low and zanubrutinib is unlikely to interfere with the anti-CD20 antibody-induced antibody-dependent cellular cytotoxicity (ADCC) effect.
In vitro, ex vivo, and animal studies showed that zanubrutinib had no or minimal effects on platelet activation, glycoprotein expression, and thrombus formation.

5.3 Preclinical safety data

General toxicity

The general toxicologic profiles of zanubrutinib were characterized orally in Sprague-Dawley rats for up to 6-month treatment and in beagle dogs for up to 9-month treatment.

In rat repeat dose studies up to 6-month treatment, test article related mortality was noted at the dose of 1,000 mg/kg/day (81x clinical AUC) with histopathologic findings in the gastrointestinal tract. Other findings were mainly noted in the pancreas (atrophy, fibroplasia, haemorrhage, and/or inflammatory cell infiltration) at the doses ≥ 30 mg/kg/day (3x clinical AUC), in the skin around the nose/mouth/eyes (inflammatory cell infiltration, erosion/ulcer) from the dose of 300 mg/kg/day (16x clinical AUC), and in the lung (presence of macrophages in the alveolar) at the dose of 300 mg/kg/day. All these findings were fully or partially reversed after a 6-week recovery except for the pancreatic findings which were not considered clinically relevant.

In dog repeat dose studies up to 9-month treatment, test article related findings were mainly noted in the gastrointestinal tract (soft/watery/mucoid stool), skin (rash, red discoloration, and thickened/ scaling), and in the mesenteric, mandibular, and gut associated lymph nodes and spleen (lymphoid depletion or erythrophagocytosis) at the doses from 10 mg/kg/day (3x clinical AUC) to 100 mg/kg/day (18x clinical AUC). All these findings were fully or partially reversed after a 6-week recovery.

Carcinogenicity/genotoxicity

Carcinogenicity studies have not been conducted with zanubrutinib.
Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (Chinese hamster ovary) 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, 100 and 300 mg/kg/day. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The dose of 100 mg/kg/day is approximately 13-fold higher than the human therapeutic exposure.

Embryo-foetal 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 with the incidence of 0.3%-1.5%) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5-fold higher than the human therapeutic exposure.

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 70 mg/kg is approximately 25-fold higher than the human therapeutic exposure and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose 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 approximately 5-fold higher than the human therapeutic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate (E487)
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)

Printing ink

Shellac glaze (E904)
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

BeiGene Ireland Limited.
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland
Tel. +353 1 566 7660
E-mail bg.ireland@beigene.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1576/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus, Stamullen, Co Meath, K32 YD60, Ireland

BeiGene Germany GmbH
Georges-Köhlerstr. 2, 79539 Lörrach, Germany

BeiGene Netherlands B.V.
Evert van de Beekstraat 1, 104, 1118 CL Schiphol, The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- Obligation to conduct post-authorisation measures
  The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further confirm the efficacy and safety of zanubrutinib in patients with R/R MZL, the MAH will submit the final study report of the post-authorisation efficacy study (PAES): Study BGB-3111-308: a global, multicenter, phase 3, open-label, randomized study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with relapsed/refractory marginal zone lymphoma (NCT05100862).	by Q4 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

BRUKINSA 80 mg hard capsules
zanubrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 80 mg of zanubrutinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BeiGene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380, Ireland
Tel. +353 1 566 7660
E-mail bg.ireland@beigene.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1576/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BRUKINSA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

BRUKINSA 80 mg hard capsules
zanubrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 80 mg of zanubrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BeiGene Ireland Limited
10 Earlsfort Terrace
Dublin 2
D02 T380, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1576/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

BRUKINSA 80 mg hard capsules
zanubrutinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BRUKINSA is and what it is used for

BRUKINSA is an anticancer medicine that contains the active substance zanubrutinib. It belongs to a class of medicines called protein kinase inhibitors. This medicine works by blocking Bruton's tyrosine kinase, a protein in the body that helps cancer cells grow and survive. By blocking this protein, BRUKINSA reduces the number of cancer cells and slows down the worsening of the cancer.

BRUKINSA is used to treat Waldenström's macroglobulinaemia (also known as lymphoplasmacytic lymphoma), a cancer affecting a type of white blood cells called B lymphocytes or B cells that make too much of a protein called IgM. This medicine is used when the disease has come back, or treatment has not worked or in patients who cannot have chemotherapy together with an antibody.

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BRUKINSA is also used to treat marginal zone lymphoma. This is a type of cancer that also affects B lymphocytes or B cells. In marginal zone lymphoma, the abnormal B cells multiply too quickly and live for too long. This may cause enlargement of organs that are part of body's natural defences such as lymph node and spleen. The abnormal B cells may also affect various organs, such as stomach, salivary gland, thyroid, eyes, lungs, bone marrow and blood. Patients may have fever, weight loss, tiredness and night sweats, but also symptoms that depend on where the lymphoma develop. This medicine is used when the disease has come back, or treatment has not worked.

BRUKINSA is also used to treat chronic lymphocytic leukaemia (CLL), another type of cancer affecting B cells that involves the lymph nodes. This medicine is used in patients who have not

previously been treated for CLL or when the disease has come back or has not responded to previous treatment.

2. What you need to know before you take BRUKINSA

Do not take BRUKINSA

- if you are allergic to zanubrutinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking BRUKINSA:

- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section **"Other medicines and BRUKINSA"**). If you have had recent surgery or plan to have surgery, your doctor may ask you to stop taking BRUKINSA for a short time (3 to 7 days) before and after your surgery or dental procedure
- if you have an irregular heartbeat or have a history of irregular heartbeat or severe heart failure, or if you have any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have ever been advised that you are at higher risk of infections. You may experience viral, bacterial, or fungal infections during treatment with BRUKINSA with the following possible symptoms: fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice).
- if you have ever had or might have hepatitis B. This is because BRUKINSA could cause hepatitis B to become active again. Patients will be carefully checked by their doctor for signs of this infection before treatment is started
- if you have liver or kidney problems
- if you have recently had any surgery, especially if it might affect how you absorb food or medicines from your stomach or gut
- if you recently had low counts of red blood cells, infection-fighting cells or platelets in your blood
- if you had other carcinomas in the past including skin cancer (e.g., basal cell carcinoma or squamous cell carcinoma). Please use sun protection

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

Tests and check-ups before and during treatment

Laboratory tests may show lymphocytosis, an increase in white blood cells (lymphocytes) in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before and during the treatment and in rare cases the doctor may give you another medicine. Talk to your doctor about what your test results mean.

Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Children and adolescents

BRUKINSA should not be used in children and adolescents, because it is unlikely to work.

Other medicines and BRUKINSA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because BRUKINSA may affect the way some medicines work. Also, some medicines can affect the way BRUKINSA works.

BRUKINSA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes medicines such as:

- acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen and naproxen,
- anticoagulants such as warfarin, heparin and other medicines for treating or preventing blood clots,
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking BRUKINSA.

Also tell your doctor if you take any of the following medicines – The effects of BRUKINSA or other medicines may be influenced if you take BRUKINSA together with any of the following medicines:

- antibiotics to treat bacterial infections – ciprofloxacin, clarithromycin, erythromycin, nafcillin or rifampicin
- medicines for fungal infections – fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- medicines for HIV infection – efavirenz, etravirine, indinavir, lopinavir, ritonavir, telaprevir
- medicine to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression – fluvoxamine, St. John's wort
- medicine called kinase inhibitors for treatment of other cancers – imatinib
- medicines for high blood pressure or chest pain – bosentan, diltiazem, verapamil
- heart medicines/anti-arrhythmics – digoxin, dronedarone, quinidine
- medicines to prevent seizures, to treat epilepsy, or to treat a painful condition of the face called trigeminal neuralgia – carbamazepine, mephenytoin, phenytoin
- medicines for migraines and cluster headaches - dihydroergotamine, ergotamine
- medicine for extreme sleepiness and other sleep problems - modafinil
- medicine for psychosis and Tourette disorder - pimozide
- medicines for anaesthesia – alfentanil, fentanyl
- medicines called immunosuppressive agents – ciclosporin, sirolimus, tacrolimus

BRUKINSA with food

Grapefruit or Seville oranges (bitter oranges) should be consumed with caution around the time you take BRUKINSA. This is because they can increase the amount of BRUKINSA in your blood.

Pregnancy and breast-feeding

Do not get pregnant while you are taking this medicine. BRUKINSA should not be used during pregnancy. It is not known if BRUKINSA will harm your unborn baby.

Women of childbearing age must use a highly effective method of birth control during treatment with BRUKINSA and for least one month after treatment. A barrier method of contraception (e.g., condoms) must be used with hormonal contraceptives such as birth control pills or devices.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine. BRUKINSA may pass into breast milk.

Driving and using machines

You may feel tired or dizzy after taking BRUKINSA, which may affect your ability to drive or use machines.

BRUKINSA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take BRUKINSA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 320 mg (4 capsules) each day, *either* as 4 capsules once daily *or* 2 capsules in the morning and 2 in the evening.
Your doctor may adjust the dose.
Take the capsules by mouth with a glass of water with food or between meals.
Take the capsules about the same time each day.
BRUKINSA works best when it is swallowed whole. Therefore, swallow the capsules whole. Do not open, break or chew them.

If you take more BRUKINSA than you should

If you take more BRUKINSA than you should, talk to a doctor straight away. Take the capsule packet and this leaflet with you.

If you forget to take BRUKINSA

If you miss a dose, take it at the next scheduled time with a return to the normal schedule. If you take BRUKINSA once per day, take your next dose the following day. If you take the medicine twice a day, in the morning and in the evening and you forgot to take it in the morning, take your next dose in the evening. Do not take a double dose to make up for a forgotten capsule. If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking BRUKINSA

Do not stop taking this medicine unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking BRUKINSA and tell a doctor straight away if you notice any of the following side effects:

- itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)

- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath, frequent and painful urination – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), pneumonia, or urinary tract.
- dizziness
- cough
- bruising or increased tendency of bruising; contusions
- bleeding
- blood in urine
- diarrhoea; your doctor may need to give you a fluid and salt replacement or another medicine
- constipation
- skin rash
- muscle and bone aches
- fatigue
- high blood pressure
- blood tests showing a reduced number of blood cells. Your doctor should do blood tests during treatment with BRUKINSA to check the number of your blood cells.

Common (may affect up to 1 in 10 people)
- infection of the lung (lower respiratory tract infection)
- reactivation of Hepatitis B (if you had experienced Hepatitis B, it may come back)
- small bleeding spots under the skin
- nosebleed
- fast heart rate, missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- weakness
- itching of the skin
- swollen hands, ankles or feet
- low white blood cell count with fever (febrile neutropenia)

Uncommon side effects (may affect up to 1 in 100 people)
- intestinal bleeding (blood in stool)

- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)

Unknown:
- Redness and shedding of skin over a large area of the body, which may be itchy or painful (exfoliative dermatitis generalised)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store BRUKINSA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What BRUKINSA contains

- The active substance is zanubrutinib. Each hard capsule contains 80 mg of zanubrutinib.
- The other ingredients are:
  - capsule content: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate (E487), silica colloidal anhydrous and magnesium stearate. See section 2 “BRUKINSA contains sodium”.
  - capsule shell: gelatin and titanium dioxide (E171)
  - printing ink: shellac glaze (E904), iron oxide black (E172) and Propylene glycol (E1520).

What BRUKINSA looks like and contents of the pack

BRUKINSA is a white to off-white hard capsule of 22 mm in length, marked with “ZANU 80” in black ink on one side.

The capsules are provided in a plastic bottle with a child resistant closure. Each bottle contains 120 hard capsules.

Marketing Authorisation Holder

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for zanubrutinib, the scientific conclusions of CHMP are as follows:

In view of available data on dermatitis exfoliative generalised from spontaneous reporting including one case with a close temporal relationship, a positive de-challenge and re-challenge, the PRAC considers a causal relationship between zanubrutinib and dermatitis exfoliative generalised is at least a reasonable possibility. The PRAC concluded that the product information of products containing zanubrutinib should be amended accordingly.

In view of available data on febrile neutropenia from clinical trials, the PRAC considers a causal relationship between zanubrutinib and febrile neutropenia is at least a reasonable possibility. The PRAC concluded that the product information of products containing zanubrutinib should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for zanubrutinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing zanubrutinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.