Taiwan Food and Drug Administration

Assessment Report

Trade Name：百悅澤膠囊 80 毫克 /
BRUKINSA Capsules 80 mg

Active Ingredient：Zanubrutinib

License Number：MOHW-PI 028160

Applicant：臺灣百濟神州有限公司

Approval Date：2021.9.13

Indication：

(1) Zanubrutinib 適用於先前曾接受至少一種治療的被套細胞淋巴瘤 (Mantle Cell Lymphoma, MCL)成年病人。
(2) Zanubrutinib 適用於先前曾接受至少一種治療的華氏巨球蛋白血症(Waldenström's macroglobulinemia, WM)成年病人，或者用於不適合接受化學免疫治療病人的一線治療。

(1) Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
(2) Indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy or who are considered unsuitable for standard chemoimmunotherapy.

Background Information

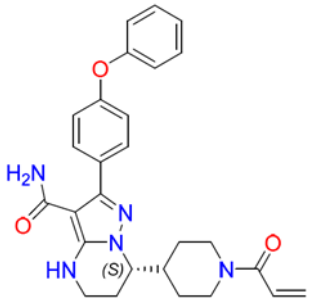
Trade Name	百悅澤膠囊 80 毫克 / BRUKINSA Capsules 80mg
Active Ingredient(s)	Zanubrutinib
Applicant	臺灣百濟神州有限公司
Dosage Form & Strengths	膠囊劑 80 mg
Indication	Zanubrutinib 適用於先前曾接受至少一種治療的被套細胞淋巴瘤 (Mantle Cell Lymphoma, MCL)成年病人。 Zanubrutinib 適用於先前曾接受至少一種治療的華氏巨球蛋白血症(Waldenström's macroglobulinemia, WM)成年病人，或者用於不適合接受化學免疫治療病人的一線治療。 Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy or who are considered unsuitable for standard chemoimmunotherapy.
Posology	每顆膠囊包含 80 mg Zanubrutinib，建議劑量為每天一次口服 320 mg (四顆 80 mg 膠囊)； 或每天兩次，每次口服 160 mg (兩顆 80 mg 膠囊) 直至疾病惡化或出現無法耐受的毒性。
Pharmacological Category **ATC Code**	L01EL03

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, zanubrutinib, is chemically designated as (7*S*)-2-(4-phenoxyphenyl)-7-[1-(prop-2-enoyl)piperidin-4-yl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide. The chemical structure of zanubrutinib is shown below:



It is a white to off-white powder. The molecular formula and the molecular weight are $C_{27}H_{29}N_5O_3$ and 471.55 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The specification of the drug substance includes tests for appearance, identification, assay, related substances, chiral purity, residual solvents, water content, loss on drying, residue on ignition, elemental impurities, polymorphic form and particle size distribution.

2.1.2 Drug product

The drug product is supplied for oral administration with the strength that contains 80 mg of zanubrutinib.

The excipients used in the drug product formulation comply with the compendial monographs.

The specification of the drug product includes appearance, identification, assay, impurities, content uniformity, dissolution, water content, chiral purity and microbial limits. Analytical methods are described well and validated.

Stability studies of the drug product under long term condition (25°C/60% RH), intermediate condition (30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Zanubrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). It forms an irreversible covalent bond ay Cys481 within the ATP binding pocket of the BTK to inhibit the activity of BTK. The *in vitro* pharmacology studies measured the IC_{50} of zanubrutinib and proved that zanubrutinib inhibited hematologic cancer cell proliferation by inhibiting BTK autophosphorylation and blocking downstream PLCγ2 signaling. The *in vivo* pharmacology studies used xenograft models to prove the zanubrutinib's inhibition effect on tumor growth of MCL and DLBCL cell lines.

The PK/PD profile indicated that zanubrutinib was quickly absorbed and eliminated. The BTK

inhibition in both PBMC and spleen occurred in a time-dependent manner. The secondary pharmacology studies indicated that zanubrutinib was more selective than ibrutinib. Zanubrutinib did not exhibit significant pharmaceutical effects on CNS, cardiovascular, and respiratory systems at the NOAEL dose levels in rats or dogs.

2.2.2 Toxicological Studies

Most findings in the repeated-dose toxicity studies in rats and dogs were slight and recoverable. For an anti-cancer drug, these findings could be considered not adverse. After daily oral administration for at least 26 weeks, the NOAEL values were 300 mg/kg in rats and 100 mg/kg in dogs.

The fertility and early embryonic development (FEED) study also indicated that zanubrutinib did not affect reproductive function at the same NOAEL as in the repeated-dose study in rats. The results of embryo-fetal development (EFD) studies suggested that zanubrutinib did not exhibit teratogenic effect at up to 150 mg/kg in rabbits but might cause visceral malformation in rats. In the pre- and postnatal developmental (PPND) study in rats, zanubrutinib did not exhibit significant adverse effects on the offspring generation at up to 150 mg/kg. Ophthalmic lesions presented in both control and treatment groups, and the dose-dependence was indistinct. Therefore, it was unclear whether the lesions were treatment-related or not.

The *in vitro* and *in vivo* genotoxicity studies presented negative results. The carcinogenicity study was not conducted based on the ICH S9 guideline. No specific local tolerance study was conducted since zanubrutinib was orally administered. However, some GI tract-related findings were observed at the dose higher than NOAEL. The mutagenicity of the impurities identified in zanubrutinib drug substance and/or drug product was evaluated, and all presented negative results. The selection of the clinical dose and dosing frequency was supported by the clinical studies.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Pharmacokinetics of zanubrutinib in patients after single-dose and multiple-dose administrations were assessed at doses from 40 mg to 320 mg once a day and 160 mg twice a day. The absolute bioavailability of zanubrutinib was not determined. Following oral administration, the median t_{max} was 2 hrs. There was a dose proportional increase in C_{max} and $AUC_{0-\infty}$ from 40 to 320 mg. Following multiple-dose administrations, limited systemic accumulation was observed. There is no clinically significant food effect on zanubrutinib. Zanubrutinib is approximately 94% bound to human plasma proteins, and the blood-to-plasma ratio was 0.7 to 0.8. The geometric mean apparent steady-state Vz/F was 522 L.

Zanubrutinib is primarily metabolized by CYP3A enzymes. There are no major active metabolites in circulation. Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, ~87% of the dose was recovered in feces (38% unchanged) and 8% in urine (<1% unchanged). Zanubrutinib is rapidly eliminated, with a mean half-life between 2 and 4 hours.

2.3.2 Interaction Studies

A dedicated DDI study indicated that co-administration of zanubrutinib with the strong CYP3A inducer rifampin decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0\text{-}inf}$, and 12.6-fold for C_{max}. Co-administration of zanubrutinib with the strong CYP3A inhibitor itraconazole increased exposure of zanubrutinib by 3.8-fold for $AUC_{0\text{-}inf}$ and by 2.6-fold for C_{max}. Additionally, PBPK simulations suggest that co-administration of multiple doses of a moderate CYP3A inhibitor (eg, fluconazole, diltiazem, and erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold. Exposure increases were < 1.5-fold with a mild CYP3A inhibitor. PBPK simulations suggest that a moderate CYP3A inducer (eg, efavirenz) may decrease the C_{max} and AUC of zanubrutinib by approximately 2- to 3-fold. The analysis showed that co-administration with PPIs and ARAs did not appear to significantly impact the PK of zanubrutinib.

Zanubrutinib had a weak induction effect on CYP3A and CYP2C19 isoenzymes. $AUC_{0\text{-}t}$ and C_{max} values, were approximately 47% and 30% lower, respectively, when midazolam (CYP3A substrate) was coadministered with zanubrutinib. $AUC_{0\text{-}t}$ and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole (CYP2C19 substrate) was coadministered with zanubrutinib. Repeated dosing of 160 mg twice a day of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for $AUC_{0\text{-}t}$ and 34% for C_{max}.

2.3.3 Special Populations

A population PK model based on 632 subjects enrolled in 9 clinical studies in patients with B-cell malignancies and healthy volunteers showed that the PK of zanubrutinib did not appear to be impacted by intrinsic factors such as age, body weight, sex, and ethnic factors.

A dedicated hepatic impairment study (Study BGB-3111-107) showed that there was no substantial difference in PK parameters between patients with mild/moderate hepatic impairment (Child-Pugh classification) and healthy subjects. The total and unbound AUC of zanubrutinib in subjects with severe hepatic impairment were 1.60- and 2.9-fold higher compared to healthy controls.

Mild and moderate renal impairment (CrCL > 30 mL/minute as estimated by Cockcroft-Gault equation) had no influence on the exposure of zanubrutinib based on population PK analysis.

Clinical PK data in patients with severe renal impairment or with ESRD populations are limited.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Mantle Cell Lymphoma (MCL)

Study BGB-3111-206 (a single-arm, open-label, multicenter Phase 2 study) and Study BGB-3111-AU-003 (a Phase 1/2, open label, multiple dose, dose escalation and expansion study) were reviewed to evaluate the efficacy of zanubrutinib indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who received at least 1 prior therapy. Independent Review Committee-assessed overall response rate was the primary efficacy endpoint and was similar in both studies. In Study BGB-3111-206, the overall response rate was 83.7% (95% CI: 74.2% to 90.8%; $p < 0.0001$ with respect to the null hypothesis of 40%), meeting the primary objective of the study. In Study BGB-3111-AU-003, the overall response rate was 81.1% (95% CI: 64.8% to 92.0%). The median duration of progression free were 22.1 months in Study BGB-3111-206 and 17.3 months in Study BGB-3111-003.

Waldenström's Macroglobulinemia (WM)

Study BGB-3111-302 (a Phase 3, randomized, open-label, multicenter study) was reviewed to evaluate the efficacy of zanubrutinib compared with ibrutinib in patients with Waldenström's Macroglobulinemia (WM). For eligibility, patients must either have had relapsed/refractory (RR) disease or had been treatment-naïve (TN) but considered by their treating physician to be unsuitable for standard chemoimmunotherapy regimens. Subjects were assigned to either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT/missing}$) based on the mutational status of the MYD88 gene.

The study was designed to test for superiority in VGPR/CR rate and noninferiority in major response rate of zanubrutinib versus ibrutinib both in Cohort 1. The testing for the primary endpoint of VGPR or CR rate superiority required testing in the relapsed/refractory analysis set prior to testing in the ITT analysis set. The proportions of Cohort 1 patients who achieved VGPR or CR were 28.9% in the zanubrutinib arm and 19.8% in the ibrutinib arm. While numerically higher rates of VGPR or CR in zanubrutinib arm were seen across analysis sets, the primary endpoint was not significant in the relapsed/refractory analysis set (estimated difference between the two rates of 10.7%, 95% CI: -2.5% to 23.9%; 2-sided $p = 0.1160$). Thus, the study did not meet the primary efficacy endpoint. In the ITT analysis set for overall WM patients (Cohort 1+2), the risk difference of VGPR or CR rate between zanubrutinib and ibrutinib was estimated as 10.2% (95% CI: -1.5% to 22.0%; 2-sided p-value = 0.0921). Although the non-inferiority of major response rate was not met in either population, PFS analysis demonstrated zanubrutinib over ibrutinib at 30 months (84.9% vs 77.6%). OS at 30 months were 90% in both groups.

In Study BGB-3111-302 Cohort 2, the proportions of patients who achieved VGPR or CR in the zanubrutinib treatment groups was 26.9%. In the supportive Study BGB-3111-AU-003, the proportion of patients who achieved VGPR or CR was 45.2%.

2.4.2 Safety Results

Mantle Cell Lymphoma (MCL)

The incidence of common adverse events was generally similar between the total R/R MCL (N=123) and integrated safety patient pools (N=641). In the integrated safety patient pool, adverse events reported in > 10% of patients were upper respiratory tract infection (34.2%), neutrophil count decreased (25.6%), rash (25.3%), bruising(23.4%), diarrhoea (20.0%), cough (19.7%), musculoskeletal pain (19.3%), pneumonia (17.6%), anaemia (15.3%), platelet count decreased (13.6%), urinary tract infection (12.8%), hematuria(12.0%), white blood cell count decreased (11.1%), fatigue (11.5%), constipation (10.9%), and hemorrhage (10.3%). In the integrated safety patient pool, 57.7% of patients experienced Grade 3 or higher adverse events. The most frequently reported Grade 3 or higher adverse events were infections (particularly respiratory infections) and peripheral blood cytopenias (neutrophil count decreased, anemia, and neutropenia).

Waldenström's Macroglobulinemia (WM)

In Study BGB-3111-302 Cohort 1(N=101), AEs reported in > 10% of patients treated with zanubrutinib were: neutropenia (24.8%); upper respiratory tract infection (23.8%); diarrhea(20.8%); fatigue (18.8%); constipation (15.8%), nausea and headache (14.9% each);dyspnea and back pain (13.9% each); epistaxis, cough, rash, pyrexia, arthralgia, contusion, and dizziness (12.9% each); anemia (11.9%); and nasopharyngitis, pain in extremity and hypertension (10.9% each). In the all WM group(N=253), AEs reported in > 20% of patients were upper respiratory tract infection (32.4%) and diarrhoea (21.7%). In the all WM group, ≥ Grade 3 adverse events reported in ≥ 5% of patients were neutropenia (11.1%), decreased neutrophil count (8.7%), anaemia (7.1%), and hypertension (5.1%).

The safety trend was consistent among all studies for MCL and WM. Compared to MCL3001 for ibrutinib, AEs of cardiac events (especially atrial fibrialltion), and GI symptoms (especially diarrhea), were less reported in patients treated with zanubrutinib. The AEs were consistent in all age groups in MCL patients but increased by age in patients with WM. Asians tended to have more AEs of cytopenia, probably related to the difference on body weight.

2.5 Bridging Study Evaluation

An PK/PD assessment of potential ethnic differences between Asian and non-Asian subjects were conducted based on: (1) the comparison of intensive PK data in patients with R/R B-cell

malignancies after a single-dose and multiple-dose administrations at the proposed clinical dose of 160 mg twice a day in studies BGB-3111-AU-003 and BGB-3111-1002; (2) a comparison of intensive PK data within Study BGB-3111-104 in healthy volunteers; (3) a population PK analysis.

In Study BGB-3111-104, similar exposures were observed between Asian (N=8) and non-Asian healthy subjects when zanubrutinib was administered alone over a range of doses (20 mg, 320 mg). Within Study BGB-3111-AU-003, zanubrutinib AUC0-inf in Asian patients (N=15) was approximately 15% higher compared with non-Asian patients. A cross-study comparison demonstrated that the exposures in Asian patients (N=34) in Study BGB-3111-1002 was numerically lower compared with non-Asian patients in Study BGB-3111-AU-003. Combining the data for Asian patients from both studies, the AUC0-inf in Asian patients (N=49) was 24.5% lower than in the non-Asian patients. At steady-state trough levels, there was comparable BTK occupancy between Asians and non-Asians. Furthermore, the population PK analysis showed that race does not significantly affect exposure of zanubrutinib. Overall, race is not a sensitive factor on zanubrutinib PK and PD.

Zanubrutinib was designated as "少數嚴重疾病" by "小兒或少數嚴重疾病藥品審查認定要點". The pivotal study for MCL (Study 206) was conducted in China and 100% of patients were Chinese. The pivotal study for WM (Study 302) was a global trial, in which only 4 Asian participants was enrolled.

The assessment of Study 206 was referred to Efficacy Section .The bridging data for WM might be partly evaluated from the ongoing Study 210, which has been conducted in R/R WM in China. Only interim safety analysis was available now. The mean age in Study 210 was 64.7-year-old in total 44 Chinese patients. The majority had MYD88L265P mutation. The median duration of exposure was 516.0 days (16.95 months). Half of patients had SAEs and 72.7% of patients had Grade >=3 AEs. The most common AEs were cytopenia and upper respiratory tract infection. All SAEs reported > 1 patients were respiratory infection except 2 patients had skin infection. This safety profile was similar among pivotal studies, where Asian patients had more cytopenia and infection, probably because of relative low body weight.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The submitted clinical data demonstrated a favorable risk-benefit profile with adequate evidence to recommend regular approval for the following indication:

(1) Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

(2) Treatment of adult patients with Waldenström's macroglobulinemia who have received at least one prior therapy or who are considered unsuitable for standard chemoimmunotherapy.

3. Post-Marketing Requirements

(1) Submit the final report of FDA-required PMR 3735-1 and PMR 3735-3 after study completion.

(2) Provide the drug consumption data and estimate drug demand in Taiwan during 5 years after approval to fulfill the requirement of 小兒或少數嚴重疾病藥品審查認定要點.