Taiwan Food and Drug Administration

Assessment Report

Trade Name：衛徠膜衣錠 / VELEXBRU Tablets 80mg

Active Ingredient：Tirabrutinib Hydrochloride

License Number：MOHW-PI 028193

Applicant：台灣小野藥品工業股份有限公司

Approval Date：2021/10/29

Indication：

成人復發或難治型原發性中樞神經系統 B 細胞淋巴瘤。

Relapsed or refractory B-cell primary central nervous system lymphoma in adult patients.

Background Information

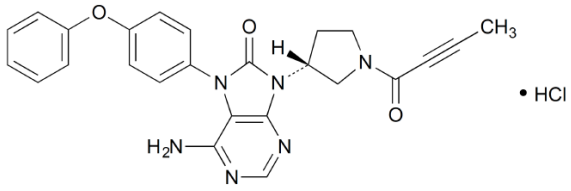
Trade Name	衛徠膜衣錠/ VELEXBRU Tablets 80mg
Active Ingredient(s)	Tirabrutinib Hydrochloride
Applicant	台灣小野藥品工業股份有限公司
Dosage Form & Strengths	Film-coated tablets 80mg
Indication	成人復發或難治型原發性中樞神經系統 B 細胞淋巴瘤。 Relapsed or refractory B-cell primary central nervous system lymphoma in adult patients.
Posology	每日一次 480 毫克 (空腹時使用) 480 mg once daily (administration in the fasting state)
Pharmacological Category **ATC Code**	

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, tirabrutinib hydrochloride, is chemically designated as 6-amino-9-[(3*R*)-1-(but-2-ynoyl)pyrrolidin-3-yl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one monohydrochloride. The molecular formula and the relative molecular mass for tirabrutinib hydrochloride are $C_{25}H_{22}N_6O_3 \cdot HCl$ and 490.94 g/mol, respectively. The chemical structure of tirabrutinib hydrochloride is shown below:



It is a white to pale yellow or pale brown powder. The structure of tirabrutinib hydrochloride is confirmed by elemental analysis, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, UV spectrum and mass spectrum. In addition, the three-dimensional structure of tirabrutinib is confirmed by single crystal X-ray diffraction. The specification for the drug substance includes tests for description, identity, assay and purity.

2.1.2 Drug product

The drug product is supplied for oral use as film coated tablets containing 80 mg tirabrutinib (equivalent to 86.42 mg tirabrutinib hydrochloride). All excipients are well known

ingredients and suitable for proposed formulation. The specification for the drug product includes description, identity, assay, purity, uniformity of dosage units and dissolution. Analytical methods are described well and validated. Stability studies of drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Velexbru® (Tirabrutinib HCl) is a drug for the treatment of relapsed or refractory primary central nervous system lymphoma. Tirabrutinib is a Bruton's tyrosine kinase (BTK) inhibitor, which blocks the signal transduction of B-cell receptors. In the in vitro studies, tirabrutinib selectively and irreversibly inhibited BTK auto-phosphorylation by covalent binding to cysteine in the active site. Tirabrutinib inhibits the growth of diffuse large B-cell lymphoma (DLBCL) cells both in vitro and in vivo and inhibits cellular functions of human basophils, neutrophils, and monocytes in vitro. Safety pharmacology studies indicated that tirabrutinib affected CNS and induced ataxic gait, decreased locomotor activity, and lost nociception.

2.2.2 Toxicological Studies

In the repeated-dose toxicity studies in rats, daily oral administration of 1000 mg/kg of tirabrutinib affected the CNS and caused death. Hemorrhage, inflammation, and fibrosis in the pancreas were the major histopathological findings to determine the NOAEL in male rats. Minimal to slight hemorrhage in pancreas also occurred in the lower-dose groups in monkeys but not in the high-dose group. These findings in monkeys were not dose-dependent and considered not related to test article. Previous studies have indicated that the pancreatic toxicity of small molecular BTK inhibitor is specific to rats and not relevant to other species including human. The genotoxicity studies indicated that tirabrutinib had no mutagenic or clastogenic effect. Diffuse degeneration of the seminiferous tubules was observed in monkeys at 100 mg/kg PO QD for 4 weeks. Embryo-fetal mortality in rats and rabbits and incidence of teratogenicity in rats were increased in the high-dose groups. Although the exposure of the high-dose groups is higher than clinical exposure, tirabrutinib should be used in pregnant women only if the expected benefits outweigh the risks. Tirabrutinib did not induce skin irritation in vitro but might induce skin sensitization in mice. The in vitro study indicated that tirabrutinib had no phototoxicity.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

In Japanese patients with relapsed or refractory primary central nervous system lymphoma, 480 mg of this drug was repeatedly administered orally once daily in the fasted state; the pharmacokinetic parameters of C_{max} were 1760 ± 929 ng/mL on Day 1 and 2690 ± 1120

ng/mL on Day 28, respectively, and the AUC_{24h} were 9830 ± 2650 ng*h/mL on Day 1 and 13400 ± 3910 ng*h/mL on Day 28, respectively.

The ratios of the geometric mean values of C_{max} and AUC_{inf} (postprandial/fasting) were 1.74 and 1.29, respectively, after oral administration of 320 mg of this drug to 12 healthy Japanese adults after meal (standard diet) and in the fasted state.

The human serum protein binding rate of tirabrutinib was 92% and the blood/plasma concentration ratio in human was 0.71–0.83.

The primary metabolic enzyme of tirabrutinib was CYP3A4 (*in vitro*). When a single dose of ^{14}C-tirabrutinib 75 mg was administered to 8 healthy adults in the fasted state, M33 (sulfate conjugates of hydroxide), M12 (glucuronide conjugates of hydroxide), and unchanged tirabrutinib were mainly detected in plasma up to 24 h after administration (accounting for 33.1%, 28.6%, and 17.3%, respectively, of the total plasma radioactivity).

When a single dose of ^{14}C-tirabrutinib 75 mg was administered to 8 healthy adults in the fasted state, 52.2% and 42.1% of the administered radioactivity were excreted in the feces and urine, respectively, up to 360 h after administration. No unchanged tirabrutinib was detected in the urine up to 96 h after administration.

2.3.2 Interaction Studies

When 20 mg of tirabrutinib in combination with 200 mg of itraconazole (CYP3A inhibitor) or tirabrutinib alone was administered to 12 healthy Japanese adults after meal, the ratios (combination to single administration) of geometric means of C_{max} and AUC_{inf} of tirabrutinib were 1.24 and 1.49, respectively.

When 100 mg of tirabrutinib in combination with a single dose of 600 mg of rifampicin (organic anion transporter polypeptide [OATP] 1B1/1B3 inhibitor) or tirabrutinib alone was administered to 15 healthy adults in the fasted state, the ratios (combination to single administration) of least-square geometric means of C_{max} and AUC_{inf} of tirabrutinib were 1.30 and 1.11, respectively. When 100 mg of tirabrutinib after repeated administration of 600 mg of rifampicin as an inducer of CYP3A or tirabrutinib alone was administered in the fasted state, the ratios (combination to single administration) of least-square geometric means of C_{max} and AUC_{inf} of tirabrutinib were 0.30 and 0.29, respectively.

When 100 mg of tirabrutinib in combination with 20 mg of omeprazole (gastric acid secretion inhibitor) or tirabrutinib alone was administered to 12 healthy adults in the fasted state, the ratios (combination to single administration) of least-square geometric means of

C_{max} and AUC_{inf} of tirabrutinib were 0.92 and 1.05, respectively.

When 2 mg of midazolam (CYP3A4 substrate) after repeated administration of 320 mg tirabrutinib or midazolam alone was administered to 12 healthy Japanese adults after meal, the ratios (combination to single administration) of geometric means of C_{max} and AUC_{inf} of midazolam were 0.74 and 0.79, respectively.

Tirabrutinib is a substrate of P-glycoprotein (P-gp), and inhibited P-gp, OATP1B1, and multidrug and toxin extrusion (MATE) 1 (*in vitro*).

2.3.3 Special Populations

The effects of covariates on PK parameters (ka, CL/F, and V2/F) were evaluated by a population PK analysis. In conclusion, Japanese or non-Japanese, sex, concomitant use of a CYP3A4 inhibitor, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and cancers were not incorporated for CL/F, and Japanese or non-Japanese was not incorporated for V2/F. Although body weight was incorporated in CL/F and V2/F and dose was incorporated in ka as covariates, the effect of body weight on PK is not considered clinically meaningful.

The impact of renal impairment on the pharmacokinetics of tirabrutinib has not been evaluated in clinical studies in patients with renal impairment. Renal excretion was not the main route of elimination for tirabrutinib in a mass balance study, and renal function was not selected as a significant covariate in the population PK analysis. Therefore, no dose adjustment associated with renal impairment was considered necessary.

The effect of hepatic impairment on the pharmacokinetics of tirabrutinib has not been evaluated in clinical studies in patients with hepatic impairment. Although hepatic function was not a significant covariate in the population PK analysis, the elimination of tirabrutinib was considered to be proceeded primarily by hepatic metabolism according to the mass balance study. Therefore, caution is needed when taking this drug in patients with hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of tirabrutinib was based on the results of Study ONO-4059-02 which was a Japan only, phase 1/2 trial among patients with relapsed or refractory primary central nervous system lymphoma (PCNSL). In the Phase II study part, efficacy and safety of tirabrutinib were investigated in an open-label, uncontrolled manner. There were total 44 patients receiving tirabrutinib 320 mg (n=20), 480 mg (n=7, early termination), or 480mg fasting

(n=17). The overall response rate (ORR) by central review in the 480mg fasting group were 52.9% (95%CI: 27.8, 77.0). The lower limit of 95%CI exceeded the pre-specified threshold of ORR 14.0%. Similar results were demonstrated by investigator' assessment (secondary endpoint). The updated duration of response (DOR) and progression-free survival (PFS) data in the 480mg fasting group were 12.88 months and 7.39 months respectively. Overall survival was not mature. The 480mg fasting group was better than the 320mg group on efficacy.

2.4.2 Safety Results

The safety data of 44 patients with median (min to max) duration of exposure 81.5 (25 to 588) days in Study ONO-4059-02 was limited. The most common adverse events of the system organ class (SOC) were "gastrointestinal disorders", "investigations", "infections and infestations", and "blood and lymphatic system disorders", with the most common preferred terms of rash (31.8%), neutrophil count decreased (13.6%), and erythema multiforme (11.4%). Most of these events were of mild to moderate severity. Infection, severe skin disorder, marrow depression, hypersensitivity, interstitial lung diseases, and hepatic impairment were identified as important risks with Grade≧3 adverse drug reaction observed. These events were consistent with the known safety profile of BTK inhibitors. The post-marketing safety updates in Japan, with an estimated cumulative patient exposure of 211 patient-years, revealed no new safety signals.

2.5 Bridging Study Evaluation

In a population PK analysis, the ethnicity was not selected as a covariate for apparent clearance (CL/F) and central volume of distribution (V2/F) of tirabrutinib. Besides, the exposure (Cmax and AUC) of tirabrutinib in Japanese patients with B-NHL and CLL was compared with that in non-Japanese patients. Although the exposure tended to be slightly higher in Japanese patients than in non-Japanese patients, the slight exposure difference would be within the inter-individual variability of tirabrutinib PK. Based on the above, the PK of tirabrutinib in plasma was considered not to differ greatly in Asian and non-Asian patients.

From clinical perspective, R/R PCNSL is a rare and life-threatening disease. Currently, there is no standard treatment for R/R PCNSL. Study ONO-4059-02 was conducted in Japan only and Asian clinical data was provided. Therefore, it is expected ethnic difference will cause no clinical impact.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of tirabrutinib (Velexbru®) was demonstrated by ORR and durable

response in adult patients with relapsed or refractory B-cell primary central nervous system lymphoma. For PCNSL, ORR is considered a potential surrogate endpoint which is reasonably likely to predict a clinical benefit. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

The overall benefit/risk ratio is favorable to support accelerated approval of the claimed indication.

3. Post-Marketing Requirements

- This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. We agree the design of Study ONO-4059-09 as the confirmatory trial.
-Submit the final report of Study ONO-4059-02 and Study ONO-4059-09 after study completion.
- Submit special drug use results survey for relapsed or refractory PCNSL in Japan while available.
-Provide drug consumption data and estimate drug demand in Taiwan during the 5 years after approval to fulfill the requirement of Rare and Severe Disease Designation.