Taiwan Food and Drug Administration

Assessment Report

Trade Name： Alunbrig® film-coated tablets 90 mg

Active Ingredient：Brigatinib

License Number：MOHW-PI 027731

Applicant：台灣武田藥品工業股份有限公司

Approval Date：2019/08/26

Indication：
ALUNBRIG 適用於在 crizotinib 治療中惡化或無法耐受之 ALK 陽性的晚期非小細胞肺癌(NSCLC)患者。

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

1. Background Information

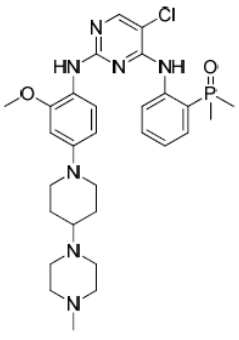
Trade Name	癌能畢® 膜衣錠 90 毫克/ Alunbrig® film-coated tablets 90 mg
Active Ingredient(s)	brigatinib
Applicant	台灣武田藥品工業股份有限公司
Dosage Form & Strengths	film-coated tablets 90mg
Indication	ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. ALUNBRIG 適用於在 crizotinib 治療中惡化或無法耐受之 ALK 陽性的晚期非小細胞肺癌(NSCLC)患者。
Posology	90 mg orally once daily for the first 7 days;if 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.
Pharmacological Category ATC Code	L01XE43

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Brigatinib is an off-white to beige, non-hygroscopic solid.



Brigatinib is achiral. The structure of brigatinib has been confirmed using ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), single crystal X-ray crystallography, elemental analysis, Fourier transform infrared (FT-IR) spectroscopy, and ultraviolet (UV) spectroscopy.

The drug substance specifications were based on the drug substance critical quality attributes

(CQAs), which include suitable test items to confirm the quality. The analytical methods used have been adequately described and non-compendial methods appropriately validated.

2.1.2 Drug product

The drug product is presented as white to off-white film-coated tablets in 30 mg, 90 mg and 180 mg dose strengths. Strengths can be distinguished by their shape, size and debossing. The core tablets of the three dosage strengths are proportional in composition. All excipients are well known ingredients and suitable for proposed formulation.

The manufacturing process contains common steps for coated tablets to obtain drug product. The drug product specifications include appropriate tests for film-coated tablets dosage form. The analytical methods used have been adequately described and appropriately validated. Drug product may be packaged in either HDPE screw cap bottles or Aclar / foil blisters. Stability studies of drug product under long term condition (30℃/75% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The active ingredient of Alunbrig is brigatinib. Brigatinib potently inhibited the kinase activity of ALK and a series of ALK variants in vitro. Brigatinib inhibited cell growth and phosphorylation/downstream signaling of ALK in cells bearing different ALK variants. The antitumor activity of brigatinib was demonstrated in mice bearing cell lines expressing ALK variants. Also, brigatinib had a potent inhibitory effect on some types of ROS1 and EGFR variants, and reduced the tumor growth in xenograft mouse models.

According to the overall kinase inhibitory profile of brigatinib, a subset of the kinases with evidence of potent or modest inhibitory activity by brigatinib was identified. Among them, 2 kinases with a high degree of structural similarity to ALK and several kinases known to have oncogenic activity were further characterized. Brigatinib inhibited IGF-1R and INSR with potency approximately 30-fold lower and 2000-fold lower, respectively, than it inhibited ALK. Brigatinib had a moderate to weak inhibitory effect on FLT3, RET, HER2 and some of their variants. In an in vitro receptor binding selectivity screen, 10 μM brigatinib exhibited minimal off-target activity against a panel of secondary pharmacology targets.

Safety pharmacology studies with brigatinib did not indicate any potential for QT prolongation or neuro-functional effects up to the highest dose examined, but identified potential for pulmonary effects, cardiovascular effects, and renal effects.

2.2.2 Toxicological Studies

High dose of brigatinib caused mortality and severe toxicity in rats and monkeys; no NOAELs could be determined in the chronic toxicity studies in both species. A variety of target organ toxicities were observed in rats and/or monkeys, which were generally reversible and considered to be monitored clinically. Irreversible testicular and ocular effects were noted only in rats but not in monkeys.

Brigatinib manifested teratogenic effects in the high dose group in rats. Brigatinib did not show any evidence of genotoxic activity in the bacterial reverse mutation assay or in the in vitro mammalian chromosome aberration test. On the other hand, brigatinib demonstrated potential to be genotoxic by inducing chromosomal damage in rats. A single dose study on eye and skin in pigmented rats showed no phototoxicity for brigatinib up to the highest dose examined. The general toxicology studies in rats and monkeys provide toxicological coverage for the metabolite, AP26123.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). It inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling protein STAT3 in *in vitro* and *in vivo* assays. Brigatinib is indicated for the treatment of patients with ALK-positive advanced non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The recommended dosage for brigatinib is 90 mg orally once daily for the first 7 days; if tolerated, increase to 180 mg orally once daily. It may be taken with or without food.

The geometric mean (CV%) steady-state C_{max} of brigatinib at the doses of 90 mg and 180 mg once daily was 552 (65%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding $AUC_{0\text{-}Tau}$ was 8165 (57%) ng·h/mL and 20276 (56%) ng·h/mL. After a single dose and at steady state, systemic exposure of brigatinib was dose proportional over the dose range of 60 mg to 240 mg once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Brigatinib is 91% bound to human plasma proteins and the binding is not concentration-dependent. The blood-to-plasma concentration ratio is 0.69. Following oral administration of brigatinib 180 mg once daily, the mean apparent V_z/F of brigatinib at steady-state was 153 L.

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 *in vitro*. And the primary route of excretion of brigatinib is in faeces. Following oral administration of a single 180 mg dose

of radiolabeled brigatinib, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively. The mean apparent CL/F of brigatinib at steady-state is 12.7 L/h and the mean plasma elimination half-life is 25 hours.

2.3.2 Interaction Studies

The results of drug-drug interaction studies showed that the strong CYP3A inhibitor increased brigatinib C_{max} by 21% and $AUC_{0\text{-}INF}$ by 101%, and the strong CYP3A inducer decreased brigatinib C_{max} by 60% and $AUC_{0\text{-}INF}$ by 80%. Strong CYP2C8 inhibitor also decreased brigatinib C_{max} by 41% and $AUC_{0\text{-}INF}$ by 12%. The PBPK stimulations indicated that the moderate CYP3A inhibitor was predicted to increase the AUC of brigatinib by approximately 40% and the moderate CYP3A inducer was predicted to decrease the AUC of brigatinib by approximately 50%. *In vitro* studies showed that brigatinib was an inducer of CYP3A and an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K.

2.3.3 Special Populations

Based on the population PK analysis, age, race, sex, body weight, and albumin concentration had no clinically relevant impact on the pharmacokinetics of brigatinib. In subjects with severe hepatic impairment (Child-Pugh C), the unbound brigatinib $AUC_{0\text{-}INF}$ was 37% higher than healthy subjects with normal hepatic function, while the pharmacokinetics of brigatinib was similar between healthy subjects and patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

In subjects with severe renal impairment (CL_{cr} = 15 to 29 mL/min), the unbound brigatinib $AUC_{0\text{-}INF}$ was 86% higher than healthy subjects with normal renal function. The brigatinib exposures were similar between healthy subjects and patients with mild (CL_{cr} 60 to 89 mL/min) or moderate (CL_{cr} 30 to 59 mL/min) renal impairment based on a population PK analysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, a Phase II, randomized, open-label, active-controlled study was provided to support the efficacy of brigatinib film-coated tablets, indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

The primary efficacy endpoint was the confirmed ORR, as assessed by the investigators per RECIST v1.1. The investigator-assessed confirmed ORR was 44.6% (97.5% CI: 34.0%, 55.6%) for 90 mg QD group and 54.5% (97.5% CI: 43.5%, 65.3%) for 90 mg -> 180 mg

group. As both lower limits of the 2-sided 97.5% CI exceeded pre-defined margin of 20% for both groups, the prospectively defined criteria for efficacy were met. Similar results were obtained from the IRC-assessed confirmed ORRs: 49.1% (97.5% CI: 39.5%, 58.7%) for 90 mg QD group and 53.6% (97.5% CI: 43.9%, 63.2%) for 90 mg -> 180 mg group.

2.4.2 Safety Results

Based on the pivotal Phase II study, there were total 219 patients who received at least one dose of brigatinib. Of them, 110 patients received the dosing regimen as the label. The median duration of exposure was 469 days in total patients and 522 days in the group with label posology. The most common (≥ 20%) adverse reactions were nausea, diarrhea, vomiting, headache, cough, fatigue, blood CPK increased, decreased appetite, dyspnea, constipation, and hypertension.

Specific AEs known to be associated with ALK inhibitor included interstitial lung disease/pneumonitis, hypertension, hepatotoxicity, bradycardia, visual disturbance, pancreatic event, elevated CPK, and hyperglycemia. Early onset pulmonary events (EOPEs) were identified in the first-in-human study and were observed at higher incidences with higher starting doses (≥120mg QD). In the pivotal Phase II study, 6.4% (14/219) of patients had EOPEs and the median time of onset was day 2 after initiation of 90mg treatment. 3.2% of (7/219) patients had Grade≥3 EOPEs and all discontinued from the treatment.

The common (≥ 30%) laboratory abnormalities were AST increased, glucose increased, CPK increased, ALT increased, amylase increased, lipase increased, and hemoglobin decreased. In summary, the safety profile of brigatinib for the treatment of ALK positive NSCLC was acceptable.

2.5 Bridging Study Evaluation

From PK perspective, the ethnic comparison study was conducted in healthy Japanese and Caucasian. The study results showed that the brigatinib $AUC_{0\text{-}inf}$ and C_{max} ratio for Japanese vs Caucasian was 0.85 and 0.96, respectively, which indicated there were no clinically meaningful differences in brigatinib PK in Japanese subjects as compared with Caucasian subjects. Population PK analysis also demonstrated the brigatinib exposures were similar between Asian and Caucasian subjects. Overall, race is not a sensitive factor on brigatinib PK.

From clinical perspective, bridging data for efficacy and safety was mainly from subgroup analysis of the pivotal Phase II study. There were 69 Asians enrolled (31.1% of overall subjects). The proportion of patients who continued receiving drugs by cut-off date was comparable between Asian and Non-Asian subgroups. The investigator-assessed confirmed

ORR, post-hoc HR in PFS showed no substantial difference between these 2 subgroups. Any death was reported in a lower proportion of Asian patients. TEAEs were reported in a similar proportion of Asian and Non-Asian patients. SAE were reported in a lower proportion of Asian patients. In summary, the efficacy results and safety profiles in Asian population were comparable to those observed in Non-Asian population. The ethnic factor of brigatinib showed no significantly clinical impact.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of brigatinib was demonstrated by a durable ORR in patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib enrolled in a randomized, open-label, active-controlled study. For NSCLC, 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 not required to ensure that the benefits of the drug outweigh the risks.

In conclusion, the overall benefit/risk ratio is favorable to support accelerated approval of the claimed indications.

3. Post-Marketing Requirements

Submit the CSR of the confirmatory study [Study AP26113-13-301: comparing brigatinib vs. crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy] after completion.