Taiwan Food and Drug Administration

Assessment Report

Trade Name： **LORVIQUA Film-Coated Tablets 25mg**

Active Ingredient：Lorlatinib

License Number：MOHW-PI 027691

Applicant：美商惠氏藥廠（亞洲）股份有限公司台灣分公司 / WYETH-AYERST (ASIA) LTD.

Approval Date：2019/07/18

Indication：

LORVIQUA is indicated for the treatment patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) treated with (1) crizotinib and at least one other ALK inhibitors (TKIs) or (2) alectinib or ceritinib as the first ALK inhibitor therapy for advanced non-small cell lung cancer (NSCLC).

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

LORVIQUA 適用於 ALK 陽性之晚期非小細胞肺癌(NSCLC)病人在使用 (1)crizotinib 和後續至少一種其他的 ALK 抑制劑或 (2) 以 alectinib 或 ceritinib 做為第一種 ALK 抑制劑治療非小細胞肺癌發生惡化。

本適應症係依據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

1. Background Information

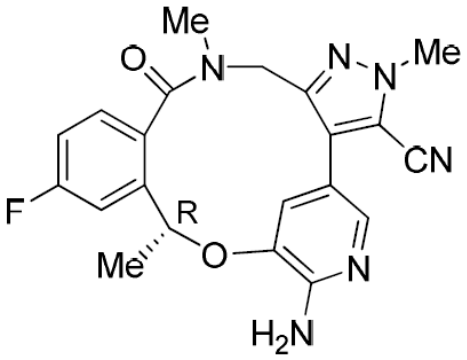
Trade Name	LORVIQUA Film-Coated Tablets 25mg
Active Ingredient(s)	Lorlatinib
Applicant	WYETH-AYERST (ASIA) LTD.
Dosage Form & Strengths	Film-Coated Tablets 25mg
Indication	LORVIQUA is indicated for the treatment patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) treated with (1) crizotinib and at least one other ALK inhibitors (TKIs) or (2) alectinib or ceritinib as the first ALK inhibitor therapy for advanced non-small cell lung cancer (NSCLC). This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. LORVIQUA 適用於 ALK 陽性之晚期非小細胞肺癌(NSCLC)病人在使用(1)crizotinib 和後續至少一種其他的 ALK 抑制劑或(2)以 alectinib 或 ceritinib 做為第一種 ALK 抑制劑治療非小細胞肺癌發生惡化。 本適應症係依據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。
Posology	The recommended dosage of LORVIQUA is 100 mg orally once daily, with or without food, until disease progression or unacceptable toxicity. LORVIQUA 的建議劑量為口服 100 毫克，每日一次，可伴隨或不伴隨食物服用，直到疾病惡化或發生無法耐受的毒性。
Pharmacological Category ATC Code	L01XE44

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, lorlatinib, is chemically designated as (10*R*)-7-amino-12-fluoro-2, 10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8- methenopyrazolo[4,3-*h*] [2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile and has the following structure:



It is white to off white powder. The molecular formula and the molecular weight are $C_{21}H_{19}FN_6O_2$ and 406.41, respectively. The structure has one chiral center. Lorlatinib is non-hygroscopic.

Adequate information of characterization of the drug substance has been provided. The structure of lorlatinib is confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography and mass spectrometry (MS). The specification for the drug substance includes tests for appearance, particle size, identification, residual solvents, water content, residue on ignition, organic impurities and assay.

2.1.2 Drug product

Lorlatinib tablet (LORVIQUA Film-Coated Tablets) is a tablet contained 25 mg of drug substance packaged in a foil/foil blister or HDPE bottle. All compendial excipients and all individual components of coating material used in the drug product formulation comply with compendial monographs. The established operating parameters and test results are acceptable.

The release specification for the drug product includes appearance, identification, assay, degradation products, uniformity of dosage units, dissolution and microbial enumeration tests. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25℃/60% RH and 30℃/75% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro, lorlatinib demonstrated potent, concentration-dependent inhibition of ALK, ALK mutants, and ROS1 kinases. Lorlatinib also inhibited ALK and ROS1 dependent oncogenic functions in human NSCLC cell lines, demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines expressing ALK and ROS1 fusion variants or ALK fusions containing clinically relevant secondary kinase domain mutations.

In vivo, lorlatinib demonstrated marked tumor growth inhibition in mice bearing tumor xenografts that express ALK or ROS1 fusion variants. Lorlatinib treatment significantly reduced tumor size and prolonged animal survival in orthotopic brain models in mice. The antitumor efficacy of lorlatinib was dose dependent and demonstrated a strong correlation to inhibition of ALK or ROS1 phosphorylation.

Safety pharmacology studies conducted in rats and dogs identified the potential for lorlatinib to cause cardiovascular, neurofunctional, and respiratory effects. Lorlatinib was identified as a weak inhibitor of hERG potassium current and of L-type calcium channels and increased late sodium currents. A single dose of lorlatinib in rats was associated with increases in systolic, diastolic, and mean blood pressure and caused a biphasic response in heart rate. Single-dose lorlatinib administration to dogs was associated with increased heart rate and decreased systolic blood pressure, and QRS and PR interval prolongation. The potential for mild, non-dose dependent impairment of cognitive function in rats was identified in a contextual renewal mode. Single doses of lorlatinib given to rats transiently caused lower mean tidal volumes, with no observed effects on respiratory rate or minute volume.

2.2.2 Toxicological Studies

Lorlatinib was administered to rats and dogs in toxicity studies up to 13 weeks in duration with BID dosing. Moribundity preceded by clinical signs of intolerance was observed in repeat-dose toxicity studies at 60 mg/kg/day in rats and 50 mg/kg/day in dogs where systemic exposure exceeded exposure at clinically relevant doses. Based on the nonclinical safety studies conducted with lorlatinib, the important toxicities included changes associated with inflammation across multiple tissues, and changes in the pancreas, hepatobiliary system, male reproductive system, cardiovascular system, and gastrointestinal tract of rats and dogs.

Additional important findings were observed in peripheral nerves, CNS, and the kidney of rats. Other lorlatinib-related findings that were considered of less importance were observed in the hematolymphopoietic system (not related to inflammation), changes in lipid profiles in rats and dogs, and alterations in body weight and food consumption in rats. Reversibility (full or partial) was established for all lorlatinib-related target organ toxicities with the exception

of hepatic bile duct hyperplasia after 13 weeks of lorlatinib administration in rats. Lorlatinib was also associated with the potential for embryo-fetal toxicity and was identified as an aneugen.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Lorlatinib, a kinase inhibitor, is indicated for the treatment of adults patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). The recommended dosage is 100 mg orally once daily.

The mean lorlatinib absolute bioavailability is 80.78% after oral administration compared to intravenous administration. The median lorlatinib T_{max} was 1.2 hours (0.5 to 4 hours) following a single oral 100 mg dose and 2 hours (0.5 to 23 hours) following 100 mg orally once daily at steady state. The lorlatinib C_{max} increases proportionally and AUC increased slightly less than proportionally over the dose range of 10 mg to 200 mg orally once daily, this may be due to autoinduction of lorlatinib. High fat, high calorie meal had slightly increased AUC by 5%, but decreased C_{max} by 9%, thus, lorlatinib can be taken regardless of food.

The plasma protein binding ratio was 0.66 (66%) at 2.4 μM. The blood-to-plasma ratio was 0.99. The geometric mean steady state volume of distribution (V_{ss}) of lorlatinib was 305 L following 50 mg intravenous administration to healthy subjects. Lorlatinib can cross the blood-brain barrier in rats, dogs and human studies. Mean CSF/free plasma ratios in human were 0.7481 and 0.6791.

In vitro, lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3. Following a single oral 100 mg dose of radiolabeled lorlatinib, the overall mean recovery of radioactivity was 88.64% (47.73% from urine and 40.91% from feces). Urinary excretion of unchanged lorlatinib was a minor route of elimination (<1% of the administered parent drug). The half-life of lorlatinib ranged from 20.9 to 25.5 hours.

2.3.2 Interaction Studies

Lorlatinib was contraindicated with strong CYP3A inducers and should be avoided concomitant use with moderate CYP3A inducers and strong CYP3A inhibitors. If co-administered with a strong CYP3A inhibitor cannot be avoided, the dose of lorlatinib should be reduced. Besides, concomitant use with CYP3A substrates with narrow therapeutic index should be avoided.

2.3.3 Special Populations

Based on population PK analysis, the PK of lorlatinib was not affected by age, gender and body weight. In addition, mild to moderate renal impairment (CLcr 30 to 89 mL/min) and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1.5 × ULN and any AST) did not have effect on the simulated exposure of lorlatinib. Thus, no dose adjustment was required for these patients. The effect of severe renal impairment or moderate to severe hepatic impairment on lorlatinib pharmacokinetics is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The review was based on the interim clinical study report of Study B7461001(data cut-off date: 2017/9/15). Study B7461001 is an ongoing, Phase 1/2, open-label, single-arm, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamics, and antitumor activity study of lorlatinib as a single agent in patients with ALK-positive or ROS1-positive metastatic NSCLC. A total of 334 patients (55 patients in Phase 1, 276 patients in Phase 2, and 3 patients in the Japan lead-in cohort) were enrolled in Study B7461001.

Efficacy analysis set was based on 215 ALK-positive NSCLC subjects with lorlatinib 100 mg QD use. In the 100-mg QD pooled group, all patients had received prior systemic therapy and ALK inhibitor for their disease. Most subjects were either White (50.7%) or Asian (34.4%). One hundred and forty-nine subjects (69.3%) had brain metastases at study entry. The overall response rate (ORR) was 48% (95% CI: 42, 55) for overall analysis set and intracranial (IC) ORR was 60% (95% CI: 49, 70) for patients with at least 1 measurable brain lesion at baseline. The median month of duration of response (DOR) in ORR was 12.5 months. The median month of DOR in IC ORR for at least one measurable lesion was 19.5 months.

2.4.2 Safety Results

Safety analysis set was 296 subjects of the 100 mg QD pooled group. Overall, 295 patients had 3892 AEs and 107 patients (36.3%) had SAE. 23 patients (7.8%) permanently discontinued treatment in association with AEs. The most frequently reported (>20%) AEs were hypercholesterolemia (84.4%), hypertriglyceridemia (66.8%), edema (53.9%), peripheral neuropathy (47.5%), cognitive effects (27.1%), dyspnea (26.8%), fatigue (25.8%), weight increased (24.1%), arthralgia (22.7%), mood effects (22.0%), and diarrhea (21.7%). The majority of AEs were mild intensity and manageable. The most frequent (>2%) SAEs were disease progression (8.8%) and dyspnea (2.7%).

Out of 295 patients, 29 (9.8%) died on study treatment or within 28 days of their last dose of lorlatinib, and 42 (14.2%) patients died after 28 days of their last dose of lorlatinib; none of

the deaths were considered related to study drug toxicity. The most frequent reason for death was disease progression (65 patients, 22.0%).

2.5 Bridging Study Evaluation

Based on Phase 2 part of Study B7461001, the Cmax for Asian patients were higher than non-Asian patients (single dose:↑52.4%; multiple dose:↑25.07%), but the AUC were comparable between non-Asian and Asian patients. Besides, race did not have a statistically significant effect on lorlatinib PK based on the population PK analysis. In summary, lorlatinib may not be considered ethnically sensitive between Asian and non-Asian from PK perspective.

Among the efficacy analysis set of the 100mg QD Pooled Group, 74(34.4%) subjects were Asians (Japan, Taiwan, Korea, Hong Kong and Singapore). The response rate was numerically higher in the Asian subjects than the Non-Asian subjects for both ORR and IC ORR, although the CIs for these groups are overlapping. The incidence of the most adverse events was lower in the Asian subjects than that in the Non-Asian subjects or comparable to Non-Asian subjects. In summary, the efficacy results and safety profiles in Asian population were comparable to those observed in overall population.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of lorlatinib was demonstrated by a durable ORR 48% in a subgroup of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter study (Study B7461001). 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 following CSRs while available：

1. The confirmatory clinical study.
2. Hepatotoxicity study: a study which evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR agonists and non-PXR agonists) and non-CYP3A inducers (PXR agonists and non- PXR agonists) using a pharmacologically-relevant animal model capable of demonstrating the clinically observed hepatotoxicity signal.

3. Study B7461010: PK trial in patients with severe renal impairment.
4. Study B7461009: PK trial in patients with moderate and severe hepatic impairment.