Taiwan Food and Drug Administration

Assessment Report

Trade Name：Vizimpro Film-Coated Tablets 15 mg

Active Ingredient：Dacomitinib

License Number：MOHW-PI 027769

Applicant：美商惠氏藥廠（亞洲）股份有限公司台灣分公司

Approval Date： 2019/12/05

Indication：做為單一療法，適用於帶有 EGFR 突變之局部晚期或轉移性非小細胞肺癌（NSCLC）成人病人的第一線治療。

1. Background Information

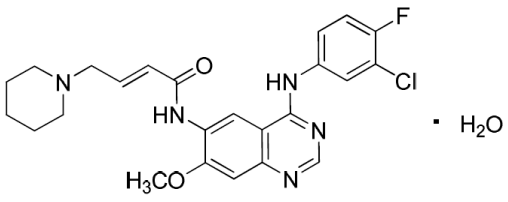
Trade Name	肺欣妥膜衣錠 15 毫克 / VIZIMPRO Film-Coated Tablets 15 mg
Active Ingredient(s)	Dacomitinib
Applicant	美商惠氏藥廠（亞洲）股份有限公司台灣分公司
Dosage Form & Strengths	膜衣錠
Indication	做為單一療法，適用於帶有 EGFR 突變之局部晚期或轉移性非小細胞肺癌（NSCLC）成人病人的第一線治療。 Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.
Posology	詳細內容請參閱仿單
Pharmacological Category **ATC Code**	L01XE47

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Dacomitinib is used as the drug substance of Vizimpro Film-Coated tablet. The drug substance has the following structure:



The molecular formula and the molecular weight are $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$ and 487.95 Daltons, respectively. It is a white to pale yellow powder.

The structure of dacomitinib is confirmed by NMR spectroscopy, mass spectrum, IR spectrum, UV/Vis spectrum, elemental analysis and X-ray crystallography. The specification includes tests for appearance, identification, assay, impurities, water

content, residual solvents, residue on ignition and particle size.

2.1.2 Drug product

Drug product is presented as film-coated tablets containing 15, 30 and 45 mg of drug substance and packaged in HDPE bottles and aluminum foil blisters. The excipients used in the drug product formulation comply with the compendial monographs or in-house specification. The established operating parameters and test results for manufacturing process are suitable.

Adequate release and shelf-life specifications have been presented for the drug product. The drug product release specification includes tests for appearance, identification, assay, impurities, dissolution, uniformity of dosage units, water content and microbial limits. Analytical methods are described and well validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Dacomitinib is a drug for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations. The *in vitro* pharmacology studies demonstrated that dacomitinib is highly selective to and the irreversibly inhibited EGFR. Among the protein kinases that share a homologous cysteine residue to EGFR-Cys797 (binding site of dacomitinib and other EGFR inhibitors), dacomitinib and its metabolite, PF-05199265, possess significant potency toward HER2 and HER4 but not the other related kinases.

The inhibition of HER2 autophosphorylation and tumor growth by dacomitinib was also demonstrated in the *in vivo* xenograft models. Dacomitinib inhibited the growth of the tumor with EGFR L858R/T790M mutation that relapsed from gefitinib or erlotinib therapy.

Safety pharmacology studies indicated that dacomitinib presented no significant effects on CNS, cardiovascular, and respiratory systems. Although the nonclinical drug-drug interaction of dacomitinib was not investigated, it was known that dacomitinib was metabolized by CYP enzymes, including CYP3A4 and CYP2D6. The inhibitors or activators of CYP enzymes might affect the pharmacokinetics of

dacomitinib.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 6-month study in rats and a 9-month study in dogs. The major target organs and findings included skin (inflammation), kidney (papillary necrosis, atrophy of tubules, dilation of pelvis), and epithelial atrophy in liver, eye, and gastrointestinal tract. The severe toxicity in the gastrointestinal tract caused loose or liquid feces, even moribundity (only in rats).

Dacomitinib presented negative results in the Ames test and *in vivo* micronucleus assay. In the *in vitro* chromosome aberration assay, dacomitinib did not induce chromosome damages but an increase of polyploidy cells in the 24-hour treatment without metabolic activation. The toxicity in embryo-fetal development was expectable since EGFR is vital in reproductive and developmental processes. Women will be recommended to use contraception during treatment and until 17 days (equal to 5 half-lives) after the final dose.

Carcinogenicity studies were not conducted since the indication is advanced cancer. The other toxicity studies indicated that dacomitinib had good compatibility with human blood, had no phototoxicity, and might stimulate histamine release from human mast cells directly. Twenty-four impurities or metabolites were examined for mutagenic potential by Ames test, and the results were used to justify the acceptance criteria in the final product.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The mean absolute bioavailability of dacomitinib is 80% and median T_{max} is 6 hours after oral administration. Steady state was achieved within 14 days following repeated dosing and the estimated accumulation ratio was 5.7. A high calorie meal did not significantly affect dacomitinib exposures. Dacomitinib PK is dose-proportional at doses ranging from 2 to 60 mg. The patients and healthy subjects possessed similar PK for dacomitinib and its active metabolite (PF-05199265).

The mean V_{ss} is 1889 L. Plasma protein binding rate for dacomitinib is approximately 98% and independent of drug concentrations. Dacomitinib is primarily metabolized by hepatic oxidation and glutathione conjugation. CYP2D6 was the major isozyme of oxidation involved in the formation of O-desmethy dacomitinib (PF-05199265) which exhibited similar *in vitro* pharmacologic activity to dacomitinib. The steady-state

trough concentration of PF-05199265 ranges from 7.4% to 19% of the parent drug. Mean terminal elimination half-life is 70.3 hours for dacomitinib. In the mass balance study, 79% of the radioactivity was recovered in feces (20% as dacomitinib) and 3% in urine (<1% as dacomitinib).

2.3.2 Interaction Studies

Rabeprazole, a PPI, decreased the mean C_{max} and $AUC_{0\text{-}96hr}$ of dacomitinib by 51% and 39%, respectively. Concomitant use of PPIs with dacomitinib should be avoided. Antacids did not cause clinically relevant changes in dacomitinib exposures. The effect of H2 receptor antagonists on dacomitinib PK has not been studied. Administer dacomitinib at least 2 hours before or 10 hours after taking an H2-receptor antagonist.

The concomitant administration of dacomitinib (a strong CYP2D6 inhibitor) with dextromethorphan (a probe CYP2D6 substrate) increased the mean AUC_{last} and C_{max} of dextromethorphan by 9.6-fold and 9.7-fold, respectively. Avoid the concomitant use of CYP2D6 substrates with a narrow therapeutic index with dacomitinib. The concomitant administration of dacomitinib with paroxetine (a strong CYP2D6 inhibitor) increased the total AUC_{last} of total drug moiety (dacomitinib +PF-05199265) in plasma by approximately 6%, which is not considered clinically relevant.

2.3.3 Special Populations

The Population PK analysis indicated that subjects with mild (n=590) and moderate (n=218) renal impairment had comparable dacomitinib exposure to patients with normal renal function (n=567). No dosage adjustment is needed in patients with mild or moderate renal impairment. Limited data are available in patients with severe renal impairment. No data are available in patients requiring hemodialysis.

In a formal PK study, the mean dacomitinib AUC_{inf} and C_{max} were comparable for subjects with mild (n=8) to moderate hepatic impairment (n=9) versus those with normal hepatic function (n=8). In addition, the Population PK analysis indicated that patients with mild (n=158) and moderate (n=5) hepatic impairment had comparable dacomitinib exposure to patients with normal hepatic function (n=1202). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on dacomitinib PK is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Sponsor provided one phase III study (A7471050) to support the efficacy of dacomitinib for the claimed indication. The efficacy findings for this study were summarized below.

- **Study [A7471050]**

This was a multinational, multi-site, randomized, open-label, Phase 3 efficacy and safety study comparing dacomitinib with gefitinib in patients with locally advanced or metastatic newly diagnosed, treatment-naive non-small cell lung cancer (NSCLC) or with recurrent NSCLC.

The primary endpoint was Progression-free survival (PFS) per blinded Independent Radiologic Central (IRC) review. Results showed that dacomitinib was superior to gefitinib in prolonging PFS as determined by blinded IRC review (HR=0.589, 95% CI: 0.469, 0.739; 1-sided p<0.0001). The key secondary endpoint was overall survival (OS). Results showed that HR was 0.760 (95% CI: 0.582, 0.993) with a 1-sided p-value of 0.0219 based on stratified analysis.

2.4.2 Safety Results

Main TEAEs include diarrhea, stomatitis/mucosal inflammation, nausea, constipation, mouth ulcer, asthenia, fatigue, paronychia, conjunctivitis, liver enzymes elevation, decreased appetite, cough, dyspnea, acneiform dermatitis, dry skin, alopecia, pruritus, rash/palmar-plantar syndrome, hypokalemia, interstitial lung disease, anemia, lymphopenia, hyponatremia, hypocalcemia, increased creatinine, hypomagnesemia and hyperbilirubinemia.

2.5 Bridging Study Evaluation

The impact of ethnic factor on dacomitinib PK was evaluated by cross-study comparison and Population PK analysis. PK exposures (C_{max} and AUC_{tau}) at steady state after multiple doses of 45 mg daily in East Asian patients were approximately 25% lower to Caucasian patients. The Population PK analysis showed that dacomitinib clearance is estimated slightly higher (8.5%) in Asian population relative to non-Asian population, but the relatively low magnitude difference is not considered clinically relevant. Overall, there appeared to be no significant ethnic difference in dacomitinib PK.

In the pivotal study A7471050, there are 346 East Asian subjects (76.5% of total). The median PFS of East Asian subjects is 16.5 months for dacomitinib and 9.3 months for gefitinib; the HR was 0.509 (95% CI: 0.391, 0.662). The median OS of

East Asian subjects is 34.2 months for dacomitinib and 29.1 months for gefitinib; the HR was 0.812 (95% CI: 0.595, 1.108). The efficacy result in East Asian subgroup is consistent with that in overall population.

In the pivotal study A7471050, the safety profile of dacomitinib is comparable between East Asians and non-East Asians; some TEAEs of dacomitinib occurred more frequent in East Asian as compared to non-East Asians: diarrhea (90.6% vs. 77.2%), rash (79.4% vs. 71.9%), stomatitis (75.9% vs. 49.1%) and liver-related laboratory tests (36.5% vs. 8.8%).

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of dacomitinib was demonstrated by significant improvement in PFS and OS in patients of locally advanced or metastatic newly diagnosed, treatment-naive NSCLC or with recurrent NSCLC with EGFR-activating mutation who were enrolled in a multinational, multicenter, randomized, open-label, active-controlled study. 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 approval.

The sponsor claimed the indication for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR TK mutations, and the mutations were not specified. Exon 19 deletion and exon 21 L858R substitution mutations are the most common types (account for 85% of EGFR mutation) which were the population in the Study A7471050. However, other rare types of mutations (such as L861Q, S768I and G719X) are increasingly reported; responses to TKIs of these uncommon mutations are not fully elucidated, some reports indicated poorer responses to TKIs as compared to classical mutations.

The mutation gene is not specified in the NSCLC indication of previously approved TKIs in this country. Since the increasing knowledge of rare EGFR mutations over time, it is recommended to add the description of limitation of EGFR mutations types based on the clinical study below the main text of indication in the label as following. *“Efficacy and safety of Vizimpro have not been established in patients with locally advanced or metastatic NSCLC whose tumor have EGFR mutations other than exon 19 deletion or exon 21 L858R substitution mutations.”*

3. Post-Marketing Requirements

(1) Routine pharmacovigilance.

(2) Results of post-marketing study A7471058 is required for determination of posology in patients with severe hepatic impairment.