Taiwan Food and Drug Administration

Assessment Report

Trade Name：

可申達 10 毫克膜衣錠 / Kerendia 10 mg film-coated tablets
可申達 20 毫克膜衣錠 / Kerendia 20 mg film-coated tablets

Active Ingredient：Finerenone

License Number： MOHW-PI 028325
MOHW-PI 028326

Applicant：台灣拜耳股份有限公司

Approval Date：2022.07.01

Indication：

用於患有第二型糖尿病(T2D)相關的慢性腎臟病(CKD)成年病人，可降低持續性腎絲球過濾率(eGFR)下降、末期腎病(ESKD)、心血管死亡、非致命性心肌梗塞以及因心衰竭住院的風險。

Kerendia is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes.

1. Background Information

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<tr><td>Posology</td><td>根據 eGFR 判定 Kerendia 的建議起始劑量：
- 若 eGFR ≥ 60 mL/min/1.73m^2，每天 1 次 20 毫克；
- 若 eGFR ≥ 25 至< 60 mL/min/1.73m^2，每天 1 次 10 毫克；
- 若 eGFR < 25 mL/min/1.73m^2，不建議使用。
Kerendia 目標每日劑量為 20 毫克。
The recommended starting dose of Kerendia is based on eGFR:
<table>
<tr><th>eGFR (mL/min/1.73m^2)</th><th>Starting Dose</th></tr>
<tr><td>≥ 60</td><td>20 mg once daily</td></tr>
<tr><td>≥ 25 to < 60</td><td>10 mg once daily</td></tr>
<tr><td>< 25</td><td>Not recommended</td></tr>
</table>
The target daily dose of Kerendia is 20 mg.</td></tr>
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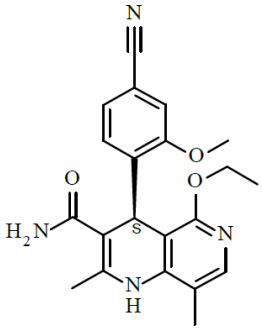
Pharmacological Category **ATC Code**	C03DA05

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, finerenone, is chemically designated as (4*S*)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide and has the following structure:



It is a white to yellow crystalline powder. The molecular formula and the molecular weight are $C_{21}H_{22}N_4O_3$ and 378.42 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of finerenone has been confirmed by IR, UV/Vis, NMR, MS, single crystal X-ray crystallography and elemental analysis.

The drug substance specification includes tests for appearance, identity, particle size, enantiomeric purity, water content, residual solvents, related substances and assay.

2.1.2 Drug Product

The drug product is an immediate release tablet for oral use. Each tablet contains 10 mg or 20 mg of finerenone. The specifications for excipients used in the drug product formulation are adequate.

The drug product specification includes appearance, identity, uniformity of dosage units, dissolution, degradation products, assay and microbial purity. Analytical methods are described well and validated.

Stability studies of the drug product under long term conditions (25°C/60% RH and 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

Finerenone has been demonstrated high *in vitro* potency and selectivity for MR and in vivo efficacy in various animal models. Finerenone was found to possess robust chronic end-organ protective efficacy of heart and kidneys at low natriuretic dosages in rats, while only much higher natriuretic dosages of the steroidal MRA eplerenone did reveal a comparable chronic end-organ protection as deduced by proteinuria, proinflammatory/-fibrotic gene expression, or histopathology. The core battery safety pharmacology studies indicated that finerenone had no effects on the CNS, cardiovascular and respiratory systems.

2.2.2 Toxicological Studies

In a 26-week study in rats and a 39-week study in dogs, finerenone was generally well-tolerated, and the toxicological profile was mainly characterized by findings directly or indirectly related to the mode-of-action and representing exaggerated pharmacology, including impairment of water and electrolyte balance, adaptive changes in the adrenals as well as the findings in the kidneys and urinary tract. The NOAELs in rats (M:5; F:1.5 mg/kg) and dogs (M:0.5; F:5 mg/kg) provided adequate safety margins for the maximum recommended human dose of 20 mg daily.

Finerenone showed no evidence of mutagenicity or genotoxicity in *in vitro* and *in vivo* studies. Reproductive and developmental studies indicated that finerenone did not impact male fertility but adversely affected female fertility and early embryonic development. It did not cause embryo-fetal lethality or juvenile toxicity, but it adversely impacted embryo-fetal development and resulted in an increase in postnatal pup mortality, delayed postnatal development, and changed neurobehaviors in the F1 generation exposed during pregnancy and lactation.

In the carcinogenicity study in mice, an increased incidence of Leydig cell adenoma was found at the high dose of 30 mg/kg/day. The NOAEL of 10 mg/kg/day provides a safety margin of 17 for this finding, which is likely also a consequence of exaggerated pharmacology resulting in hormonal imbalance. In mice, no other tumors occurred. The carcinogenicity in rats did not reveal any tumorigenic effect.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Finerenone exposure increased proportionally over a dose range of 1.25 to 80 mg (0.06 to 4 times the maximum approved recommended dosage). Steady state of finerenone was achieved after 2 days of dosing. The estimated steady-state geometric mean $C_{max,md}$ was 160

μg/L and steady-state geometric mean $AUC_{\tau,md}$ was 686 μg*h/L following administration of finerenone 20 mg to patients.

Finerenone is completely absorbed after oral administration but undergoes metabolism resulting in absolute bioavailability of 44%. Finerenone C_{max} was achieved between 0.5 and 1.25 hours after dosing. There was no clinically significant effect on finerenone AUC following administration with high fat, high calorie food.

The volume of distribution at steady-state (V_{ss}) of finerenone is 52.6 L. Plasma protein binding of finerenone is 92%, primarily to serum albumin, *in vitro*. Finerenone is primarily metabolized by CYP3A4 (90%) and to a lesser extent by CYP2C8 (10%) to inactive metabolites. The terminal half-life of finerenone is about 2 to 3 hours, and the systemic blood clearance is about 25 L/h. About 80% of the administered dose is excreted in urine (<1% as unchanged) and approximately 20% in feces (< 0.2% as unchanged).

2.3.2 Interaction Studies

Concomitant use of itraconazole (strong CYP3A4 inhibitor) increased finerenone AUC by >400%. Concomitant use of erythromycin (moderate CYP3A4 inhibitor) increased finerenone mean AUC and C_{max} by 248% and 88%, respectively. Concomitant use of amiodarone (weak CYP3A4 inhibitor) increased finerenone AUC only by 21%. Concomitant use of efavirenz (moderate CYP3A4 inducer) and rifampicin (strong CYP3A4 inducer) decreased finerenone AUC by 80% and 90%, respectively.

There was no clinically significant difference in finerenone pharmacokinetics when used concomitantly with gemfibrozil (strong CYP2C8 inhibitor), omeprazole (proton pump inhibitor), or an aluminium hydroxide and magnesium hydroxide antacid. There were no clinically significant pharmacokinetic differences for either finerenone or concomitant digoxin (P-gp substrate) or warfarin (CYP2C9 substrate). And there were no clinically significant differences in the pharmacokinetics of either midazolam (CYP3A4 substrate) or repaglinide (CYP2C8 substrate) when used concomitantly with finerenone.

2.3.3 Special Populations

There are no clinically significant effects of age (18 to 79 years), sex, race/ethnicity (White, Asian, Black, and Hispanic), or weight (58 to 121 kg) on the pharmacokinetics of finerenone. There were no clinically relevant differences in finerenone AUC or C_{max} values in patients with eGFR 15 to < 90 mL/min/1.73m^2 compared to eGFR ≥ 90 mL/min/1.73 m^2. There was also no clinically significant effect on finerenone exposure in cirrhotic patients with mild hepatic impairment (Child Pugh A). Finerenone mean AUC was increased by 38% and C_{max} was unchanged in cirrhotic patients with moderate hepatic impairment (Child Pugh B)

compared to healthy control subjects. And the effect of severe hepatic impairment (Child Pugh C) on finerenone exposure was not studied.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A randomized, multicenter, double-blind, placebo-controlled Phase 3 study (16244; also called FIDELIO-DKD) was reviewed to evaluate the efficacy of Kerendia (finerenone) in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

The primary efficacy endpoint was renal composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. The key secondary endpoint was CV composite endpoint of CV death, non-fatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

Results of the primary renal composite endpoint showed that treatment with finerenone resulted in a relative risk reduction (RRR) of 17.5% (HR=0.825 with 95% CI=[0.732; 0.928]). The primary renal composite endpoint achieved statistical significance with a log-rank p-value of 0.0014, falling below the prespecified significance level of 0.03282695. The treatment effect majorly reflected a reduction in a sustained decline in eGFR of ≥40% and progression to kidney failure. And, the number of observed renal death was too small (N = 2 in each group) to draw conclusion.

Results of the key secondary CV composite endpoint showed that treatment with finerenone resulted in an RRR of 14.0% (HR=0.860 with 95% CI= [0.747; 0.989]). The key secondary CV composite endpoint achieved statistical significance with a log-rank p-value of 0.0339, falling below the prespecified significance level of 0.04967388. The trial met its key secondary cardiovascular composite endpoint, with consistency in the composite components, except for the incidence of non-fatal stroke which was similar in both treatment arms.

Study 16244 was successful as both the primary renal and key secondary CV composite endpoints showed statistically significant results.

2.4.2 Safety Results

The safety of finerenone was mainly evaluated in Phase 3 Study FIDELIO-DKD. In this study, a total of 2827 subjects were treated with finerenone. The median duration of follow-up was 32 months and the median duration of treatment was around 27 months. Overall, SAEs occurred in 31.9% of subjects receiving finerenone and 34.3% of subjects receiving placebo. Permanent discontinuation of study drugs due to AEs occurred in 7.3% of patients treated with finerenone and 5.9% of subjects treated with placebo.

The most frequently reported AE was hyperkalemia (finerenone: 18.3%, placebo 9.0%). Subjects with low eGFR, higher serum potassium, and prior history of hyperkalemia were at a higher risk to develop hyperkalemia. Hyperkalemia led to hospitalization in 1.4% of patients receiving finerenone and 0.3% of patients receiving placebo. Permanent discontinuation due to hyperkalemia occurred in 2.3% of subjects treated with finerenone and 0.9% of subjects treated with placebo.

Other common AEs with a difference ≥ 1% between arms included glomerular filtration rate decreased (finerenone: 6.3%, placebo: 4.7%), hypotension (finerenone: 4.5%, placebo: 3.1%), and pruritus (finerenone: 3.7%, placebo: 2.6%). The incidence of worsening of renal function AEs leading to hospitalization or discontinuation were similar between arms.

2.5 Bridging Study Evaluation

A cross-study analysis, including 51 Caucasian and 45 Asian healthy subjects (27 in Japanese and 18 in Mainland Chinese), showed that the dose-normalized and body weight-normalized overall exposures ($AUC_{\tau,md,norm}$/D and $C_{max,md,norm}$/D) after multiple dosing was 29.1% higher of $AUC_{\tau,md,norm}$/D and 33.5% to 37.5% higher of $C_{max,md,norm}$/D in Asian compared to Caucasian subjects.

A population PK analysis to compare the systemic exposure of finerenone in patients with CKD in T2DM of Japanese and non-Japanese was also conducted. The dose-normalized AUC at steady state (dn-AUC_{SS}) and the dose-normalized C_{max} at steady state (dn-C_{maxSS}) were 0.4% and 7.4% higher in the Japanese population than in the global population, respectively. The population PK analysis was also performed to characterize of the PK of finerenone in HF patients of Japanese and non-Japanese with a 19% difference in dn-AUC and 23% difference in dn-C_{max} were observed. In conclusion, no significant impact of ethnicity was observed on finerenone systemic exposure parameters.

Phase 3 study FIDELIO-DKD enrolled 1097 subjects (around 19% of overall population) from East Asia, including China (n=372), Hong Kong (n=61), Japan (n=415), South Korea (n=138), and Taiwan (n=111). The results of the primary renal composite endpoint of East Asia subpopulation (HR 0.723, 95% CI: [0.568; 0.920]) was generally comparable with overall population. The proportion of subjects with treatment-emergent hyperkalemia was higher in East Asia subpopulation (finerenone: 27.4%, placebo: 18.8%) compared with overall population (finerenone: 18.3%, placebo: 9.0%) in both treatment arms. Few of the hyperkalemia AEs in East Asia subpopulation were serious (1.5%) and led to permanent discontinuation of finerenone (2.4%). No additional safety signal was identified in the East Asia subpopulation.

2.6 Conclusion

This multidisciplinary review recommends approval for Kerendia 10 mg and 20 mg film-coated tablets (finerenone) for the indication of reducing the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes.

3. Post-Marketing Requirements

No post-marketing requirement is needed.