PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR KERENDIA®

Finerenone tablets

Tablets, 10 mg and 20 mg finerenone, Oral

Aldosterone Antagonist

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TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KERENDIA (finerenone) is indicated as an adjunct to standard of care therapy in adults with chronic kidney disease (CKD) and type 2 diabetes (T2D) to reduce the risk of:

- End-stage kidney disease and a sustained decrease in estimated glomerular filtration rate,
- Cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available; therefore, an indication for pediatric use has not been authorized.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with significant differences in safety or effectiveness. However, greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

KERENDIA is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING
- who are receiving concomitant systemic treatment with medications that are strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) (see 9.4 Drug-Drug Interactions)
- with Addison's disease

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Measure serum potassium levels and estimated glomerular filtration rate (eGFR) to determine whether to initiate KERENDIA treatment and to determine the starting dose of KERENDIA.
- Patients should be adequately treated with standard of care therapy prior to initiating KERENDIA.
- After initiating, re-starting or up-titrating KERENDIA, re-measure serum potassium and eGFR at 4 weeks to determine whether to continue KERENDIA treatment and for dose adjustment (see Table 1). Re-measure serum potassium periodically and as needed based on patient characteristics and serum potassium levels (see 7 WARNINGS AND PRECAUTIONS).
- Pregnancy should be ruled out prior to KERENDIA administration and breastfeeding discontinued (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

- When developing a dosage regimen, consideration should be given to the following patient populations (see 4.2 Recommended Dose and Dosage Adjustment):
    - patients with renal impairment
    - patients with hepatic impairment
    - patients taking concomitant medications

4.2 Recommended Dose and Dosage Adjustment

The recommended target dose of KERENDIA is 20 mg once daily.

Initiation of treatment

Initiation of KERENDIA treatment is recommended when serum potassium ≤ 4.8 mmol/L. For monitoring of serum potassium, see 4.2 Recommended Dose and Dosage Adjustment, Continuation of treatment.

If serum potassium > 4.8 to 5.0 mmol/L, initiation of KERENDIA treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels (see 7 WARNINGS AND PRECAUTIONS).

Initiation of KERENDIA treatment is not recommended in patients with serum potassium > 5.0 mmol/L (see 7 WARNINGS AND PRECAUTIONS).

Measure estimated glomerular filtration rate (eGFR) to determine the starting dose. The starting dose of KERENDIA is:

- 10 mg once daily if eGFR ≥ 25 to < 60 mL/min/1.73m^2
- 20 mg once daily if eGFR ≥ 60 mL/min/1.73m^2

Initiation of KERENDIA treatment is not recommended in patients with eGFR < 25 mL/min/1.73m^2 as clinical experience is limited.

Continuation of treatment

Four weeks after initiation or re-start or up-titration of KERENDIA treatment, remeasure serum potassium and eGFR. See Table 1 to determine continuation of KERENDIA treatment and dose adjustment. Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.

Table 1 – Continuation of KERENDIA treatment and dose adjustment

Serum potassium (mmol/L)	KERENDIA dose (after 4 weeks and thereafter)
≤ 4.8	Maintain 20 mg once daily. For patients on 10 mg once daily, increase the dose to 20 mg once daily if eGFR has not decreased > 30% compared to the prior measurement.
> 4.8 – 5.5	Maintain dose.
> 5.5	Withhold KERENDIA. Restart at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.

Patients with renal impairment

Initiation of KERENDIA treatment

In patients with eGFR ≥ 25 to < 60 mL/min/1.73 m^2, the starting dose of KERENDIA is 10 mg once daily. See 4.2 Recommended Dose and Dosage Adjustment, Initiation of treatment.

There are insufficient data to support dosing recommendations for initiation of KERENDIA in patients with an eGFR < 25 mL/min/1.73m^2 (see 7 WARNINGS AND PRECAUTIONS).

Continuation of KERENDIA treatment

In patients with mild, moderate or severe renal impairment, continue KERENDIA treatment and adjust dose based on serum potassium. Measure eGFR 4 weeks after initiation to determine whether patient should be up titrated. See Table 1 and 4.2 Recommended Dose and Dosage Adjustment, Continuation of treatment.

In patients with end-stage renal disease (eGFR < 15 mL/min/1.73m^2), discontinue KERENDIA treatment as clinical experience is limited (see 7 WARNINGS AND PRECAUTIONS).

Patients with hepatic impairment

In patients with severe hepatic impairment (Child Pugh C), avoid treatment with KERENDIA as clinical experience is limited and patients with severe hepatic impairment were excluded from phase III studies (see 7 WARNINGS AND PRECAUTIONS).

In patients with moderate hepatic impairment (Child Pugh B), consider additional serum potassium monitoring and adapt monitoring according to patient characteristics (see 7 WARNINGS AND PRECAUTIONS).

Patients taking concomitant medications

In patients taking KERENDIA concomitantly with weak or moderate CYP3A4 inhibitors, potassium supplements, trimethoprim, or trimethoprim-sulfamethoxazole, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics and make KERENDIA treatment decisions as directed in Table 1. Temporary discontinuation of KERENDIA when taking trimethoprim, or trimethoprim-sulfamethoxazole, may be necessary (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Geriatric patients

No dose adjustment is required in the elderly (see 10.3 Pharmacokinetics).

4.4 Administration

For oral use, one tablet per day, at approximately the same time each day.

Tablets may be taken with a glass of water and with or without food (see 10.3 Pharmacokinetics).

Avoid taking KERENDIA with grapefruit or grapefruit juice (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

For patients who are unable to swallow whole tablets, KERENDIA tablet may be crushed and mixed with water or soft foods, such as applesauce, immediately prior to use and administered orally (see 10.3 Pharmacokinetics).

Information about excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take KERENDIA.

Sodium

KERENDIA contains less than 25 mg of sodium per tablet, which is considered low sodium and suitable for restricted sodium diets.

4.5 Missed Dose

A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the dose should be skipped, and the next dose taken as prescribed. Two doses should not be taken to make up for a missed dose.

A daily dose of 20 mg of KERENDIA must not be exceeded.

5 OVERDOSAGE

No cases of adverse events associated with finerenone overdose in humans have been reported. The most likely manifestation of overdose is anticipated to be hyperkalemia. If hyperkalemia develops, standard treatment should be initiated.

Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 10 mg, 20 mg	Cellulose microcrystalline, croscarmellose sodium, ferric oxide red (10 mg film-coated tablet), ferric oxide yellow (20 mg film-coated tablet), hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide

KERENDIA tablets are presented as either pink (10 mg) or pale yellow (20 mg) film-coated, oval oblong tablets. The tablets are marked with “10” or “20” on one side and “FI” on the other side. The product is supplied in bottles of 90 tablets and in blisters of 28 or 98 tablets.

7 WARNINGS AND PRECAUTIONS

General

Concomitant use of medications or grapefruit that affect finerenone exposure

Weak and moderate CYP3A4 inhibitors

The concomitant use of KERENDIA with weak CYP3A4 inhibitors (e.g., amiodarone and fluvoxamine) and moderate CYP3A4 inhibitors (e.g., erythromycin and verapamil) is expected to increase finerenone exposure (see 9 DRUG INTERACTIONS). Consider additional serum potassium monitoring especially during initiation of or changes to dosing of KERENDIA or the CYP3A4 inhibitor (see 4 DOSAGE AND ADMINISTRATION).

Moderate and strong CYP3A4 inducers

Avoid concomitant use of KERENDIA with moderate CYP3A4 inducers (e.g., efavirenz, phenobarbital) or strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's Wort) which are expected to markedly decrease finerenone plasma concentrations and result in reduced therapeutic effect (see 9 DRUG INTERACTIONS). Consider selection of an alternate concomitant medicinal product with no or weak potential to induce CYP3A4.

Grapefruit

Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone (see 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Hepatic

Patients with severe hepatic impairment (Child Pugh C) have not been studied and were excluded from phase III studies. Due to an expected significant increase in finerenone exposure, avoid use of KERENDIA in patients with severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION).

Due to an increase in finerenone exposure, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics in patients with moderate hepatic impairment (Child Pugh B) (see 4 DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Hyperkalemia and eGFR

Hyperkalemia (serum potassium > 5.5 mmol/L) can occur in patients with CKD and T2D and may be aggravated by therapy (e.g., ACEi, ARB or MRA). KERENDIA can cause hyperkalemia (see 8.2 Clinical Trial Adverse Reactions, Hyperkalemia).

Some patients are at a higher risk to develop hyperkalemia. Risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalemia. Consider more frequent monitoring in these patients.

Although not observed in phase III studies with KERENDIA, hyperkalemia can, in rare cases, lead to serious, sometimes fatal arrhythmias.

Initiation of KERENDIA treatment is not recommended if serum potassium > 5.0 mmol/L. If serum potassium > 4.8 to 5.0 mmol/L, initiation of KERENDIA treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels. See 4 DOSAGE AND ADMINISTRATION.

Withhold KERENDIA in treated patients if serum potassium > 5.5 mmol/L. Follow local guidelines for the management of hyperkalemia. Restart KERENDIA at 10 mg once daily if serum potassium ≤ 5.0 mmol/L. See 4 DOSAGE AND ADMINISTRATION.

Initiation of KERENDIA can cause an initial decrease in eGFR that occurs within the first 4 weeks of starting therapy, and then stabilizes.

Remeasure serum potassium and eGFR in all patients 4 weeks after initiation or re-start or up-titration of KERENDIA treatment. Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels. See 4 DOSAGE AND ADMINISTRATION.

Concomitant medications

The risk of hyperkalemia may increase with the intake of concomitant medications that may increase serum potassium (see 9 DRUG INTERACTIONS and General section of 7 WARNINGS AND PRECAUTIONS).

Concomitant treatment with other MRAs and potassium sparing diuretics was prohibited during phase III studies due to the risk of hyperkalemia.

Avoid concomitant use of KERENDIA with the following medications:

- potassium-sparing diuretics (e.g., amiloride, triamterene)
- other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, spironolactone)

Use KERENDIA with caution and monitor serum potassium when taken concomitantly with the following medications:

- potassium supplements
- trimethoprim, or trimethoprim-sulfamethoxazole. Temporary discontinuation of KERENDIA may be necessary.

Renal

The risk of hyperkalemia increases with decreasing renal function. Ongoing monitoring of renal function should be performed as needed according to standard practice (see 4 DOSAGE AND ADMINISTRATION).

Initiation of KERENDIA treatment is not recommended in patients with eGFR < 25 mL/min/1.73m^2 as clinical experience is limited (see 4 DOSAGE AND ADMINISTRATION).

Continue KERENDIA treatment with caution regarding serum potassium levels in patients who have progressed to an eGFR < 25 mL/min/1.73m^2. Due to limited clinical experience, discontinue treatment in patients who have progressed to end-stage kidney disease (eGFR < 15 mL/min/1.73 m^2) (see 4 DOSAGE AND ADMINISTRATION).

A greater risk of glomerular filtration rate decrease was observed in patients receiving KERENDIA treatment compared to placebo.

Reproductive Health: Female and Male Potential

Fertility

No human data on the effect of KERENDIA on fertility is available. Animal studies with finerenone did not indicate a risk of impaired male fertility. Animal studies with finerenone indicated impaired female fertility at exposures considered in excess (about 20 times) to the maximum human exposure (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Teratogenic Risk

Animal data have shown prenatal and postnatal developmental toxicity at exposures about 4 times those expected in human. Teratogenicity was seen at exposures about 25 times those expected in human. Placental transfer of finerenone and/or its metabolites was demonstrated in pregnant rats. The relevance for humans is unknown (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). KERENDIA should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus. If the patient becomes pregnant while taking KERENDIA, the patient should be informed of potential risks to the fetus. See 7.1 Special populations.

Women of child-bearing potential/contraception

KERENDIA may cause embryo-fetal harm when administered during pregnancy. Women of childbearing potential should use effective contraception during treatment with KERENDIA (see 7.1 Special populations and 16 NON-CLINICAL TOXICOLOGY).

7.1 Special populations

7.1.1 Pregnant Women

There are no data on the use of KERENDIA in pregnant women. Pregnant women were prohibited from entering or permanently discontinued from phase III studies should pregnancy occur. Animal studies have shown embryo-fetal developmental toxicity at exposures corresponding to 19 to 25 times the maximum human exposure. In the pre- and post-natal developmental toxicity study, maternal exposure to KERENDIA at levels about 4 times than those expected in humans, increased perinatal mortality and increased locomotor activity was found in the offspring, which may have been caused by exposure during pregnancy (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

KERENDIA should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus (see 7 WARNINGS AND PRECAUTIONS).

7.1.2 Breast-feeding

It is unknown whether finerenone or its metabolites are excreted in human breast milk. Precaution should be exercised because many drugs can be excreted in human milk. Available pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk. Rat pups exposed by this route showed adverse effects (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). A risk to the nursing infant cannot be excluded (see 7 WARNINGS AND PRECAUTIONS). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from KERENDIA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

No data are available; therefore, an indication for pediatric use has not been authorized.

7.1.4 Geriatrics

Of the 6510 patients who received KERENDIA in the FIDELIO-DKD and FIGARO-DKD studies, 40.4% were between 65 and 74 years, and 14.2% were 75 years and older. Although evidence from clinical studies has not identified significant differences in efficacy between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of KERENDIA in patients with chronic kidney disease and type 2 diabetes was evaluated in two pivotal phase III studies FIDELIO-DKD and FIGARO-DKD (see 14 CLINICAL TRIALS). In the FIDELIO-DKD study, 2833 patients received KERENDIA (10 or 20 mg once daily) with a mean duration of treatment of 2.2 years. In the FIGARO-DKD study, 3686 patients received KERENDIA (10 or 20 mg once daily) with a mean duration of treatment of 2.9 years.

Overall, serious adverse reactions occurred in 32% of patients receiving KERENDIA and in 34% of patients receiving placebo in the FIDELIO-DKD study, and in 31% of patients receiving KERENDIA and in 33% of patients receiving placebo in the FIGARO-DKD study. Permanent discontinuation due to adverse reactions occurred in 7% of patients receiving KERENDIA and in 6% of patients receiving placebo in the FIDELIO-DKD study, and 6% of patients receiving KERENDIA and in 5% of patients receiving placebo in the FIGARO-DKD study.

The most commonly reported adverse reactions (≥ 5% of patients receiving KERENDIA and higher frequency in KERENDIA) in the FIDELIO-DKD study were, hyperkalemia (18.3% of patients receiving KERENDIA vs. 9.0% of patients receiving placebo) and decreased GFR (6.3% of patients receiving KERENDIA vs. 4.7% of patients receiving placebo). The most frequently reported (≥ 5% of patients receiving KERENDIA and higher frequency in KERENDIA) adverse reaction in the FIGARO-DKD study was hyperkalemia (10.8% of patients receiving KERENDIA vs. 5.3% of patients receiving placebo). For specific recommendations, see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

In the FIDELIO-DKD study, exposure was calculated for the safety analysis set (SAF), comprising 2827 vs 2831 patients in the KERENDIA vs placebo arms, respectively. Approximately 87% of patients took study drug for at least 12 months, 58% for at least 24 months, and 25% for at least 36 months. The mean duration of exposure in FIDELIO-DKD study was 26.94 vs 27.26 months, respectively for KERENDIA vs placebo, and the mean daily dose was 15.14 vs 16.48 mg, respectively.

In the FIGARO-DKD study, exposure in the safety population (3683 and 3658 subjects in the KERENDIA and placebo arms, respectively) was balanced between the treatment arms. Approximately 91% of patients took study drug for at least 12 months, 81% for at least 24 months, and 50% for at least 36 months. The mean duration of exposure was 35.2 and 35.4 months in the KERENDIA and placebo arms, respectively, and the mean daily dose was 17.5 and 18.2 mg, respectively.

Table 3 shows adverse reactions reported in ≥ 1% of patients treated with KERENDIA in the pooled FIDELIO-DKD and FIGARO-DKD studies.

Table 3 – Adverse reactions reported in ≥ 1% of patients on KERENDIA and more frequently than placebo in phase III studies (pooled FIDELIO-DKD and FIGARO-DKD)

MedDRA System Organ Class	KERENDIA N = 6510 n (%)	Placebo N = 6489 n (%)
Blood and lymphatic system disorders		
Anemia	425 (6.5)	397 (6.1)
Metabolism and nutrition disorders		
Hyperkalemia[1]	912 (14.0)	448 (6.9)
Hyperuricemia[2]	333 (5.1)	255 (3.9)
Hyponatremia[3]	82 (1.3)	47 (0.7)
Vascular disorders		
Hypotension[4]	302 (4.6)	194 (3.9)
Skin and subcutaneous tissue disorders		
Pruritus	191 (2.9)	146 (2.2)

1 includes Blood potassium increased and Hyperkalemia
2 includes Blood uric acid increased and Hyperuricemia
3 includes Blood sodium decreased and Hyponatremia
4 includes Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension

Description of Selected Adverse Reactions

Hyperkalemia

In the FIDELIO-DKD study including patients with CKD (mean eGFR 44.3 ml/min/1.73 m^2) and T2D, hyperkalemia events were reported in 18.3% of KERENDIA-treated patients compared with 9.0% of placebo-treated patients. An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the KERENDIA arm compared to placebo, remaining stable thereafter. In the FIGARO-DKD study including patients with CKD (mean eGFR 67.8 ml/min/1.73 m^2) and T2D, hyperkalemia events were reported in 10.8% of KERENDIA -treated patients compared with 5.3% of placebo-treated patients. An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.15 mmol/L was observed in the KERENDIA group compared to placebo, which remained stable thereafter. In both studies, the majority of hyperkalemia events were mild to moderate in patients treated with KERENDIA. For specific recommendations, see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS.

Hospitalization due to hyperkalemia for the KERENDIA group was 1.4% versus 0.3% in the placebo group in the FIDELIO-DKD study, and 0.6% for the KERENDIA group versus < 0.1% in the placebo group in the FIGARO-DKD study. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving KERENDIA versus 0.9% of patients receiving placebo in the FIDELIO-DKD study, and 1.2% of patients receiving KERENDIA versus 0.4% of patients receiving placebo in the FIGARO-DKD study.

Hyperuricemia

Asymptomatic hyperuricemia was observed with a higher frequency in patients receiving KERENDIA. In the FIGARO-DKD study, an increase from baseline in mean serum uric acid of up to 0.3 mg/dL was seen

in the KERENDIA group compared to placebo, which attenuated over time. No hyperuricemia related treatment discontinuations were reported.

Hypotension

In the FIDELIO-DKD study, hypotension events were reported in 4.8% of KERENDIA-treated patients compared with 3.4% of patients receiving placebo. In the FIGARO-DKD study, hypotension events were reported in 4.5% of KERENDIA-treated patients compared with 2.7% of patients receiving placebo. In KERENDIA-treated patients, hypotension events were mostly mild or moderate in intensity, rarely led to treatment discontinuation and most of these events resolved. Events associated with hypotension, e.g., dizziness, syncope, or fall, were not more frequent in patients using KERENDIA in comparison to placebo.

In patients treated with KERENDIA, the mean systolic blood pressure decreased by 3 mmHg and the mean diastolic blood pressure decreased by 1-2 mmHg at month 1, remaining stable thereafter.

8.3 Less Common Clinical Trial Adverse Reactions

In the pooled FIDELIO-DKD and FIGARO-DKD studies, the following adverse events (regardless of causality) were observed with a frequency of less than 1% and at a higher frequency in the KERENDIA arm compared to placebo:

Immune disorders: drug hypersensitivity (0.2% KERENDIA vs 0.1% placebo)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data

Table 4 shows laboratory test abnormalities reported in ≥ 1% of patients treated with KERENDIA in the pooled FIDELIO-DKD and FIGARO-DKD studies.

Table 4 – Laboratory test abnormalities reported in ≥ 1% of patients on KERENDIA and more frequently than placebo in phase III studies (pooled FIDELIO-DKD and FIGARO-DKD)

Laboratory test Abnormalities	KERENDIA N = 6510 n (%)	Placebo N = 6489 n (%)
Glomerular filtration rate decreased[1]	348 (5.3)	274 (4.2)

1 An initial decrease in eGFR (mean 2 mL/min/1.73 m^2) attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation.

Glomerular filtration rate decreased

A greater proportion of glomerular filtration rate (GFR) decrease was observed in patients receiving KERENDIA treatment compared to placebo. In the FIDELIO-DKD study, GFR decreased events were reported in 6.3% of KERENDIA-treated patients compared with 4.7% of patients receiving placebo. In the FIGARO-DKD study, GFR decreased events were reported in 4.6% of KERENDIA-treated patients compared with 3.9% of patients receiving placebo. In both studies, GFR decreased events rarely led to hospitalization or permanent discontinuation of KERENDIA.

Hemoglobin decreased

In the FIDELIO-DKD study, a decrease in mean hemoglobin levels was observed in KERENDIA-treated patients in the first 4 months, resulting in a maximum difference of less than 0.15 g/dL between KERENDIA treatment and placebo, which levelled out by Month 28. A similar effect was observed for

hematocrit with a maximum difference of less than 0.45% at Month 4. Anemia events were reported in 7.4% of KERENDIA-treated patients compared with 6.7% of patients receiving placebo.

In the FIGARO-DKD study, a decrease in mean hemoglobin levels was observed in KERENDIA-treated patients in the first 4 months, resulting in a maximum difference of less than 0.17 g/dL between KERENDIA treatment and placebo, which levelled out by Month 28. A similar effect was observed for hematocrit with a maximum difference of approximately 0.85% at Month 4. Anemia events were reported in 5.9% KERENDIA-treated patients compared with 5.6% of patients receiving placebo.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

KERENDIA is contraindicated in patients:

- who are receiving concomitant systemic treatment with medications that are strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) (see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Finerenone is a sensitive substrate of cytochrome P450 (CYP) 3A4, which is responsible for about 90% of its metabolic clearance. Inhibitors of CYP3A4 increase finerenone exposure, with strong inhibitors expected to increase its AUC by more than 350% (AUC ratio > 4.5).

Inducers of CYP3A4 are expected to decrease finerenone exposure, with a predicted decrease in AUC by more than 90% following co-administration with a potent CYP3A4 inducer. Avoid concomitant use of KERENDIA with moderate CYP3A4 inducers (e.g., efavirenz, phenobarbital) or strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's Wort). Consider selection of an alternate concomitant medicinal product with no or weak potential to induce CYP3A4.

Finerenone had no effect *in vivo* on CYP3A4 or CYP2C8 and no effect *in vitro* on the activity of any other CYP enzyme based on clinical exposure estimates. It also did not affect uridine 5'-diphospho-glucuronosyltransferase enzymes *in vitro*.

In vitro studies indicated that permeability glycoprotein (P-gp) and breast cancer resistance protein (BCRP) may be inhibited by finerenone, and a potential to inhibit the organic anion transporting polypeptide (OATP) isoform 1B1.

In vivo, 20 mg finerenone had no clinically relevant effect on the exposure of the P-gp substrate digoxin, and the risk for clinically relevant BCRP inhibition after administration of 20 mg finerenone is low. *In vivo*, 20 mg finerenone had no clinically relevant effect on the exposure of repaglinide, a substrate of OATP1B1 and OATP1B3. Therefore, the risk for clinically relevant effects on OATP substrates is low.

Finerenone had no effect *in vitro* on the activity of bile salt export pump (BSEP), multidrug and toxin extrusion protein 1 (MATE1), multidrug and toxin extrusion protein 2K (MATE2K), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 1 (OCT1), organic cation transporter 2 (OCT2) and OATP1B3.

Effects of other substances on finerenone

Finerenone is cleared almost exclusively via cytochrome P450 (CYP)-mediated oxidative metabolism (mainly CYP3A4 [90%] with a small contribution of CYP2C8 [10%]).

Medications that increase serum potassium

It is anticipated that medications that increase serum potassium will increase the risk of hyperkalemia when used concomitantly with KERENDIA.

Concomitant use of KERENDIA with the following medications should be avoided:

- potassium-sparing diuretics (e.g., amiloride, triamterene)
- other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, spironolactone)

KERENDIA should be used with caution and serum potassium monitored when taken concomitantly with the following medications:

- potassium supplements
- trimethoprim, or trimethoprim - sulfamethoxazole. Temporary discontinuation of KERENDIA may be necessary.

Consider selection of alternate concomitant medicinal products.

See also 7 WARNINGS AND PRECAUTIONS.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

The drugs listed in Table 5 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 – Established or Potential Drug-drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical Comment
Effect of strong CYP3A4 inhibitors on finerenone			
Itraconazole (200 mg BID)	T	AUC ↑ 423-676% C_{max} ↑ 124-150%	Due to an expected marked increase in finerenone exposure, concomitant use of KERENDIA with itraconazole, clarithromycin and other strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, nelfinavir, cobicistat, telithromycin or nefazodone) is contraindicated (see 2 CONTRAINDICATIONS).
Clarithromycin (500 mg BID)	T	AUC ↑ 352-527% C_{max} ↑ 114-136%	

Proper / Common name	Source of Evidence	Effect	Clinical Comment
Effect of moderate CYP3A4 inhibitors on finerenone			
Erythromycin (500 mg thrice daily)	CT	AUC ↑ 248% C_{max} ↑ 88%	Serum potassium may increase, and therefore, additional monitoring of serum potassium is recommended and dose adjustment may be needed (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).
Verapamil (240 mg controlled-release tablet once daily)	CT	AUC ↑ 170% C_{max} ↑ 120%	
Effect of weak CYP3A4 inhibitors on finerenone			
Fluvoxamine (100 mg BID)	T	AUC ↑ 57% C_{max} ↑ 38%	Serum potassium may increase, and therefore, monitoring of serum potassium is recommended (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).
Effect of strong and moderate CYP3A4 inducers on finerenone			
Rifampicin (600 mg OD)	T	AUC ↓ 93% C_{max} ↓ 86%	Due to the expected decrease in finerenone exposure, concomitant use of KERENDIA with rifampicin and other strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, St John's Wort) or with efavirenz and other moderate CYP3A4 inducers (e.g., phenobarbital) should be avoided (see 7 WARNINGS AND PRECAUTIONS).
Efavirenz (600 mg OD)	T	AUC ↓ 81% C_{max} ↓ 68%	

Legend: C=Case Study; CT=Clinical Trial; T=Theoretical

Note: The effects of itraconazole, clarithromycin, fluvoxamine, rifampicin and efavirenz on finerenone exposure are predictions based on PBPK simulations. No clinical data was available to evaluate effects of strong and weak CYP3A4 inhibitors or strong and moderate CYP3A4 inducers on finerenone exposure.

9.5 Drug-Food Interactions

Administration of a single KERENDIA 20 mg tablet with a high-fat, high-calorie meal to healthy volunteers resulted in a decrease of C_{max} and prolonged t_{max} (2.47 h vs 0.75 h), compared to administration under fasted conditions. This was paralleled by an increase in extent of absorption (AUC). The administration of 10 mg of an earlier developmental formulation tablet exhibited a similar effect of food with a decrease in C_{max}, prolonged t_{max} (2.50 h vs 0.75 h), and increase in AUC. Administration of a single KERENDIA 20 mg tablet, crushed and re-suspended in applesauce, resulted in a decrease in AUC, a decrease of C_{max} and an earlier t_{max} (0.733 h vs 1.25 h), compared to administration of the intact tablet under fasted conditions (see 10.3 Pharmacokinetics). In phase III clinical studies finerenone was taken without regard to food. Finerenone tablets can be taken with or without food (see 4 DOSAGE AND ADMINISTRATION).

Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentration of finerenone and should be avoided (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

9.6 Drug-Herb Interactions

Avoid concomitant use of KERENDIA with St John's Wort (a strong CYP3A4 inducer) which may markedly decrease finerenone exposure and result in reduced therapeutic effect.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR). Finerenone binds to the MR and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone plays a central role in the homeostatic regulation of blood pressure, plasma sodium and potassium levels. The mechanisms of action contributing to reduction of renal and cardiovascular events with KERENDIA are not completely understood and may be due to multi-factorial effects in different tissues. Potential mechanisms of action reported under certain experimental conditions include: attenuation of inflammation and fibrosis that are thought to be mediated by MR overactivation. *In vitro*, finerenone dose-dependently inhibited MR interaction with transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators. Blocking of MR by finerenone *in vivo* counteracts sodium retention in the kidneys and hypertrophic processes in the kidneys, heart and blood vessels.

Finerenone has no relevant affinity for androgen, progesterone, estrogen and glucocorticoid receptors and therefore is unlikely to cause sex hormone-related adverse events (e.g., gynecomastia).

10.2 Pharmacodynamics

Effects in healthy participants

Multiple dose regimens of finerenone (daily doses of 20 mg or 40 mg over 10 days) led to activation of the renin-angiotensin-aldosterone system (RAAS), i.e., reversible increases of plasma renin activity and serum aldosterone concentrations with baseline values reached again within 48 hours after the last dose.

Following activation of the MR with the agonist fludrocortisone, single doses of finerenone up to 20 mg showed natriuretic effects while decreasing urinary potassium excretion as compared to placebo.

The highest single dose of 80 mg and the highest multiple dose of 40 mg of finerenone did not affect vital signs parameters in healthy participants.

Effects in patients with CKD and T2D

In randomized, double-blind, placebo-controlled, multicenter phase III studies in adults with CKD and T2D (FIDELIO-DKD and FIGARO-DKD), the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio (UACR) in patients randomized to finerenone at Month 4 was 31% and 32%, respectively and UACR remained reduced throughout both studies for at least 48 months.

In MinerAlocorticoid Receptor Antagonist Tolerability Study - Diabetic Nephropathy (ARTS DN), a randomized, double-blind, placebo-controlled, multicenter phase IIb dose-finding study in adults with CKD and T2D, the placebo-corrected relative reduction in UACR at Day 90 was 25% and 38% in patients treated with finerenone 10 mg and 20 mg once daily, respectively.

Cardiac electrophysiology

In a dedicated randomized, blinded, placebo- and positive-controlled four-way crossover QT study in 57 healthy participants, there was no indication of a clinically relevant QT/QTc prolonging effect of finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic).

10.3 Pharmacokinetics

Finerenone pharmacokinetics are linear across the investigated dose range from 1.25 to 20 mg. A summary of finerenone pharmacokinetic parameters is shown in Table 6.

Table 6 – Summary of finerenone pharmacokinetic parameters in plasma (healthy volunteers (geometric mean (geometric coefficient of variation), or median (range) for t_{max})

	C_{max} [µg/L]	T_{max} [h]	$T_{½}$ [h]	$AUC_{0-\infty}$ [µg*h/L]	CL[1] [L/h]	Vd [1] [L]
10 mg	78.1 (25.6)	0.74 (0.25-1.52)	2.31 (41.4)	198 (24.9)	22.3 (18.6)	52.6 (17.3)
20 mg	145 (34.6)	0.75 (0.50-2.48)	2.82 (43.1)	394 (26.4)		

1 calculated after intravenous infusion of 1 mg finerenone

Absorption:

Finerenone is almost completely absorbed after oral administration. Absorption is rapid with maximum plasma concentrations (C_{max}) appearing between 0.5 and 1.25 hours after tablet intake in the fasted state. The absolute bioavailability of finerenone is 43.5% due to first-pass metabolism in the gut-wall and liver. Finerenone is not predicted to be a relevant substrate of the efflux transporter P-gp *in vivo*.

Effect of Food:

Administration of a single KERENDIA 20 mg tablet with a high-fat, high-calorie meal to healthy volunteers resulted in a 19% lower C_{max} and prolonged t_{max} (2.47 h vs 0.75 h), compared to administration under fasted conditions. This was paralleled by an increase in extent of absorption (AUC) by 21%. The administration of 10 mg of an earlier developmental formulation tablet exhibited a similar effect of food with 32% lower C_{max}, prolonged t_{max} (2.50 h vs 0.75 h), and 10% increase in AUC. Administration of a single KERENDIA 20 mg tablet, crushed and re-suspended in apple sauce, resulted in an 18% decrease in AUC, an 11% decrease in peak plasma concentration and an earlier t_{max} (0.733 h vs 1.25 h), compared to administration of the intact tablet under fasted conditions (see 4 DOSAGE AND ADMINISTRATION).

Distribution:

The volume of distribution at steady state (Vss) of finerenone is 52.6 L. The human plasma protein binding of finerenone *in vitro* is 91.7%, with serum albumin being the main binding protein.

Metabolism:

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. Four major metabolites were found in plasma, resulting from oxidation of the dihydropyridine moiety to a pyridine (M1a, M1b), subsequent hydroxylation of a methyl group (M2a) and formation of a carboxyl function (M3a). All metabolites are pharmacologically inactive.

Elimination:

The elimination of finerenone from plasma is rapid with an elimination half-life ($t_{1/2}$) of about 2 to 3 hours. Excretion of unchanged finerenone represents a minor route (<1% of dose in the urine due to glomerular filtration, < 0.2% in the feces). About 80% of the administered dose was excreted via urine and approximately 20% of the dose was excreted via feces, almost exclusively in the form of metabolites. The systemic blood clearance is about 25 L/h.

Special Populations and Conditions

Pediatrics:

Safety and efficacy of KERENDIA have not been studied in children and adolescents below 18 years of age.

Geriatrics:

Of the 6510 patients who received KERENDIA in the FIDELIO-DKD and FIGARO-DKD studies, 55% of patients were 65 years and older, and 14% were 75 years and older. No overall differences in pharmacokinetic parameters were observed between these patients and younger patients (50 to 65 years). There was no adjustment of KERENDIA dose based on age during the clinical studies.

In a dedicated phase I study with healthy subjects, elderly subjects (≥ 65 years of age; n=18) exhibited higher finerenone plasma concentrations than younger subjects (≤ 45 years of age; n=18), with mean AUC and C_{max} values being 34% and 51% higher in the elderly (see 4 DOSAGE AND ADMINISTRATION).

Sex:

No clinically relevant difference in finerenone exposure was observed between females and males (see 4 DOSAGE AND ADMINISTRATION).

Ethnic origin:

A pooled interethnic analysis of finerenone in healthy subjects demonstrated about 30% and 55-75% higher dose-normalized AUC and C_{max} in Asian compared to Caucasian subjects after single dose and multiple dose administration, respectively. This difference was reduced to about 5-10% (single dose) and 30-40% (multiple dose) by normalization to body weight. Population-pharmacokinetic analyses in patients demonstrated no clinically relevant difference in finerenone exposure between Asian and Caucasian patients (see 4 DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency:

There was no clinically relevant change in finerenone exposure in cirrhotic subjects with mild hepatic impairment (Child Pugh A) (see 4 DOSAGE AND ADMINISTRATION).

In cirrhotic subjects with moderate hepatic impairment (Child Pugh B), finerenone mean AUC was increased by 38% and C_{max} was unchanged compared to healthy control subjects (see 4 DOSAGE AND ADMINISTRATION).

There are no data in patients with severe hepatic impairment (Child Pugh C) (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

Renal Insufficiency:

Mild renal impairment (CL_{CR} 60 to < 90 mL/min) did not have a clinically relevant effect on finerenone AUC and C_{max}. Compared to subjects with normal renal function (CL_{CR} ≥ 90 mL/min), the effect of moderate (CL_{CR} 30 to < 60 mL/min) or severe (CL_{CR} < 30 mL/min) renal impairment on AUC of finerenone was similar with increases by 34-36%. Moderate or severe renal impairment had no clinically significant effect on C_{max} (see 4 DOSAGE AND ADMINISTRATION).

Due to the high plasma protein binding, finerenone is not expected to be dialyzable.

Body Weight:

Population-pharmacokinetic analyses based on FIDELIO-DKD and FIGARO-DKD trials demonstrated that administration of finerenone in subjects weighing 58 kg and 60 kg, respectively (5th percentile of body weight distribution) resulted in higher AUC and C_{max} (10 to 22% and 25 to 38%, respectively) compared to subjects with a median body weight of 85 kg and 87 kg, respectively. The administration of finerenone in subjects with a higher body weight of 121 kg and 126 kg, respectively (95th percentile of body weight distribution) exhibited an opposite effect resulting in lower AUC and C_{max} (6 to 17% and 18 to 27%, respectively) compared to subjects with a median body weight of 85 kg and 87 kg, respectively. There was no adjustment of KERENDIA dose based on body weight during the clinical studies.

11 STORAGE, STABILITY AND DISPOSAL

Store bottles and blisters at room temperature 15°C to 30°C. Keep out of sight and reach of children.

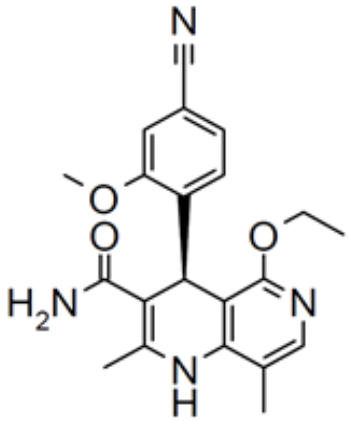
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/common name:	finerenone
Chemical name:	(4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide
Molecular formula and molecular mass:	$C_{21}H_{22}N_4O_3$ 378.42
Structural formula:	
Physicochemical properties:	Finerenone micronized drug substance is a white to yellow, crystalline powder. It is practically insoluble in water and sparingly soluble in 0.1 M HCl, ethanol, and acetone.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Renal and Cardiovascular Outcomes in Adults with CKD and T2D

Table 7 – Summary of patient demographics for clinical trials in CKD and T2D

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
FIDELIO-DKD	Randomized, double-blind, placebo-controlled, multicenter	KERENDIA 10 mg or 20 mg or placebo once daily, 27 months	KERENDIA 10 or 20 mg: n= 2833 Placebo: n= 2841	66 years (28-97)	Male: 70% Female: 30%
FIGARO-DKD	Randomized, double-blind, placebo-controlled, multicenter	KERENDIA 10 mg or 20 mg or placebo once daily, 35 months	KERENDIA 10 or 20 mg: n= 3686 Placebo: n= 3666	64 years (23-93)	Male: 69% Female: 31%

KERENDIA (finerenone) was investigated in two randomized, double-blind, placebo-controlled, multicenter phase III studies, FIDELIO-DKD and FIGARO-DKD. In these studies, the effect of KERENDIA on kidney and cardiovascular outcomes was evaluated in adults with CKD and T2D receiving either KERENDIA 10 mg or 20 mg once daily, or placebo.

Demographics and other baseline characteristics from the FIDELIO-DKD study and the FIGARO-DKD study are presented in Table 8.

Table 8 – Demographics and other baseline characteristics in phase III studies (FAS)

	FIGARO-DKD		FIDELIO-DKD	
	KERENDIA (N=3686)	**Placebo (N=3666)**	**KERENDIA (N=2833)**	**Placebo (N=2841)**
Sex: Male	2528 (68.6%)	2577 (70.3%)	1953 (68.9%)	2030 (71.5%)
Female	1158 (31.4%)	1089 (29.7%)	880 (31.1%)	811 (28.5%)
Race				
White	2672 (72.5%)	2605 (71.1%)	1777 (62.7%)	1815 (63.9%)
Black or African American	113 (3.1%)	145 (4.0%)	140 (4.9%)	124 (4.4%)
Asian	715 (19.4%)	739 (20.2%)	717 (25.3%)	723 (25.4%)
Others	186 (5.0%)	177 (4.8%)	199 (7.0%)	179 (6.3%)
Region				
Western Europe	725 (19.7%)	760 (20.7%)	619 (21.8%)	632 (22.2%)
Eastern Europe	1029 (27.9%)	990 (27.0%)	563 (19.9%)	544 (19.1%)
North America	559 (15.2%)	548 (14.9%)	467 (16.5%)	477 (16.8%)
Asia	810 (22.0%)	815 (22.2%)	790 (27.9%)	789 (27.8%)
Latin America	424 (11.5%)	417 (11.4%)	295 (10.4%)	298 (10.5%)
Others	139 (3.8%)	136 (3.7%)	99 (3.5%)	101 (3.6%)
Age (years)				
Mean	**64.13**	**64.13**	**65.44**	**65.67**
SD	9.67	10.00	8.94	9.16
Median	65.00	65.00	66.00	66.00
Baseline BMI (kg/m^2)				
Mean	**31.46**	**31.40**	**31.13**	**31.10**
SD	6.04	5.93	6.03	6.00
Q1	27.30	27.10	26.80	26.90
Median	30.70	30.60	30.40	30.30
Q3	34.70	34.80	34.30	34.50
Baseline eGFR ($mL/min/1.73m^2$)				
Arithm. Mean	**67.62**	**67.99**	**44.36**	**44.32**
Arithm.SD	21.65	21.74	12.54	12.57
Median	67.35	67.80	43.00	43.00
Baseline eGFR ($mL/min/1.73m^2$) category				
<25	15 (0.4%)	12 (0.3%)	66 (2.3%)	69 (2.4%)
25 - <45	641 (17.4%)	610 (16.6%)	1476 (52.1%)	1505 (53.0%)
45 -<60	745 (20.2%)	789 (21.5%)	972 (34.3%)	928 (32.7%)
≥60	2285 (62.0%)	2254 (61.5%)	318 (11.2%)	338 (11.9%)
Baseline UACR (mg/g)				
Geom.Mean	**284.33**	**288.87**	**798.79**	**814.73**
Geom.SD	3.58	3.53	2.65	2.67

	FIGARO-DKD		FIDELIO-DKD	
	KERENDIA (N=3686)	**Placebo (N=3666)**	**KERENDIA (N=2833)**	**Placebo (N=2841)**
Median	302.36	315.06	832.72	867.01
UACR at baseline (≤/> median in the FAS)				
≤514.7 mg/g	2397 (65.0%)	2409 (65.7%)	863 (30.5%)	842 (29.6%)
>514.7 mg/g	1289 (35.0%)	1255 (34.2%)	1968 (69.5%)	1998 (70.3%)
Baseline serum potassium (mmol/L)				
Arithm.Mean	**4.33**	**4.33**	**4.37**	**4.38**
Arithm.SD	0.43	0.43	0.46	0.46
Median	4.30	4.30	4.40	4.40
Baseline systolic blood pressure (mmHg)				
Arithm.Mean	**135.81**	**135.70**	**138.05**	**138.01**
Arithm.SD	13.96	14.06	14.32	14.42
Median	135.67	136.00	138.33	138.33
Baseline HbA1c (%)				
Arithm.Mean	**7.74**	**7.69**	**7.66**	**7.69**
Arithm.SD	1.39	1.35	1.33	1.36
Median	7.50	7.50	7.50	7.50
History of CV disease, present	1676 (45.5%)	1654 (45.1%)	1303 (46.0%)	1302 (45.8%)
Duration of diabetes (in years)				
Arithm.Mean	**14.53**	**14.44**	**16.58**	**16.55**
Arithm.SD	8.60	8.44	8.77	8.77
Median	13.18	13.90	16.12	16.15

Arithm = arithmetic, BMI = body mass index, CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, Geom = geometric, HbA1c = glycated hemoglobin, N = number of subjects, Q = quartile, SD = standard deviation, UACR = urinary albumin-to-creatinine ratio

Table 9 shows the breakdown of patients in the pooled analysis of FIGARO-DKD and FIDELIO-DKD stratified by both baseline eGFR and UACR laboratory values.

Table 9 – Number and percentage of patients by baseline eGFR and UACR in the pooled analysis of FIGARO-DKD and FIDELIO-DKD

		Urine Albumin Creatinine Ratio (UACR) categories (mg/g)		
eGFR categories (mL/min/1.73 m^2)		**<30**	**30 - <300**	**≥300**
	≥90	13 (<0.1)	198 (1.5)	1108 (8.5)
	60-89	51 (0.4)	1043 (8.0)	2780 (21.3)
	45-59	82 (0.6)	1389 (10.7)	1962 (15.1)
	30-44	68 (0.5)	1230 (9.4)	2206 (16.9)
	25-29	16 (0.1)	239 (1.8)	635 (4.9)

Values are presented at n (%)

In the pooled analysis of FIGARO-DKD and FIDELIO-DKD, 6288 (48.3%), 5354 (41.0%), 1323 (10.2%), and 64 (0.5%) of patients had very high, high, moderate, and low Kidney Disease Improving Global Outcomes (KDIGO) risk scores, respectively, according to the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.

FIDELIO-DKD STUDY

In FIDELIO-DKD patients were eligible based on evidence of persistent albuminuria (> 30 mg/g to 5,000 mg/g), an eGFR of 25 to 75 mL/min/1.73m^2, serum potassium ≤ 4.8 mmol/L at screening, and were required to be receiving standard of care, including a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Patients with diagnosed heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association II-IV) were excluded.

The primary endpoint in the FIDELIO-DKD study was a composite of time to first occurrence of kidney failure (defined as chronic dialysis or kidney transplantation, or a sustained decrease in eGFR to < 15 mL/min/1.73m^2 over at least 4 weeks), a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death. The key secondary endpoint was a composite of time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for heart failure.

The trial analyzed 5,674 patients randomly assigned to receive either KERENDIA (N=2833), or placebo (N=2841), with a median follow-up duration of 2.6 years. After the end of study notification, vital status was obtained for 99.7% of patients. The trial population was 63% White, 25% Asian and 5% Black. The mean age at enrollment was 66 years and 70% of patients were male. At baseline, the mean eGFR was 44.3 mL/min/1.73m^2, with 55% of patients having an eGFR < 45 mL/min/1.73m^2, median urine albumin-to-creatinine ratio (UACR) was 852 mg/g and mean glycated hemoglobin A1c (HbA1c) was 7.7%, 46% had a history of atherosclerotic cardiovascular disease, 30% had history of coronary artery disease, 8% had a history of cardiac failure, and the mean blood pressure was 138/76 mmHg. The mean duration of type 2 diabetes at baseline was 16.6 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 47% and 26% of patients at baseline, respectively. At baseline, 99.8% of patients were on ACEi (34%) or ARB (66%), and 97% of patients used one or more antidiabetic medications (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). The other most frequent medications taken at baseline were statins (74%) and calcium channel blockers (63%).

FIGARO-DKD STUDY

The FIGARO-DKD study included adults with CKD and T2D, based on having a UACR of ≥ 30 mg/g to <300 mg/g and an eGFR of 25 to 90 mL/min/1.73m^2, or a UACR ≥ 300 mg/g and an eGFR ≥ 60 mL/min/1.73m^2 at screening. Patients were required to have a serum potassium of ≤ 4.8 mmol/L at screening and received standard of care background therapy, including a maximum tolerated labeled dose of a renin angiotensin system (RAS) inhibitor (either an ACEi or ARB). Patients with diagnosed heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association II-IV) were excluded.

The primary endpoint of the FIGARO-DKD study was a composite of time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure. The key secondary endpoint was a composite of time to first occurrence of kidney failure, a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death.

The trial analyzed 7,352 patients randomly assigned to receive either KERENDIA (N=3686), or placebo (N=3666) that were followed for a median duration of 3.4 years. After the end of study notification, vital status was obtained for 99.8% of patients. The trial population was 72% White, 20% Asian and 4% Black. The mean age at enrollment was 64 years and 69% of patients were male. At baseline, the mean eGFR was 67.8 mL/min/1.73 m^2, with 62% of patients having an eGFR ≥ 60 mL/min/1.73 m^2, median UACR was 308 mg/g, and mean glycated HbA1c was 7.7%, 45% of patients had a history of atherosclerotic cardiovascular disease, 31% had a history of coronary artery disease, 8% had a history of cardiac failure, and the mean blood pressure was 136/77 mmHg. The mean duration of type 2 diabetes at baseline was 14.5 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 31% and 28% of patients, respectively. At baseline, 99.9% of patients were on a RAS-inhibitor and 98% of patients used one or more antidiabetic medications (insulin [54%], biguanides [69%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [8%]). The other most frequent medication class taken at baseline was statins (71%).

RESULTS

FIDELIO-DKD-STUDY

KERENDIA demonstrated superiority to placebo by significantly reducing the risk of the primary composite endpoint of a sustained decline in eGFR of ≥40%, kidney failure, or renal death compared to placebo in a time-to-event analysis using the Cox proportional hazards model and log-rank test (HR 0.82, 95% CI 0.73-0.93, p=0.0014). See Table 10 and Figure 1. KERENDIA also significantly reduced the risk of the key secondary composite endpoint of time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure compared to placebo (HR 0.86, 95% CI 0.75-0.99, p=0.0339). See Figure 2.

The treatment effect for the primary and key secondary endpoints was generally consistent across subgroups. The treatment effect for the primary was mainly driven by an effect on a reduction in sustained decrease in eGFR, though kidney failure also contributed to the treatment effect. There were few renal deaths during the trial.

Table 10 – Analysis of the primary and secondary time-to-event endpoints (and their individual components) in phase III study FIDELIO-DKD

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	KERENDIA* 10 or 20 mg OD N=2833		Placebo* N=2841		Treatment Effect	KERENDIA / Placebo
Primary and Secondary Time-to-event Endpoints:	**n (%)**	**Event Rate (100 pt-yr)**	**n (%)**	**Event Rate (100 pt-yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of kidney failure, sustained eGFR decline ≥40% or renal death	504 (17.8%)	7.59	600 (21.1%)	9.08	0.82 [0.73; 0.93]	0.0014
• Kidney failure	208 (7.3%)	2.99	235 (8.3%)	3.39	0.87 [0.72; 1.05]	-
• Sustained eGFR decline ≥40%	479 (16.9%)	7.21	577 (20.3%)	8.73	0.81 [0.72; 0.92]	-
• Renal death	2 (<0.1%)	-	2 (<0.1%)	-	-	-
Secondary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure	367 (13.0%)	5.11	420 (14.8%)	5.92	0.86 [0.75; 0.99]	0.0339
• CV death	128 (4.5%)	1.69	150 (5.3%)	1.99	0.86 [0.68;1.08]	-
• Non-fatal MI	70 (2.5%)	0.94	87 (3.1%)	1.17	0.80 [0.58;1.09]	-
• Non-Fatal stroke	90 (3.2%)	1.21	87 (3.1%)	1.18	1.03 [0.76;1.38]	-
• Hospitalization for heart failure	139 (4.9%)	1.89	162 (5.7%)	2.21	0.86 [0.68;1.08]	-

* Treatment in addition to maximum tolerated labeled doses of ACEi or ARB.

p-value: two-sided p-value from stratified logrank test

CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, N = number of subjects, n = number of subjects with event, pt-yr = patient year.

Note: Time to first event was analyzed in a stratified Cox proportional hazards model. For patients with multiple events, only the first event contributed to the composite endpoint. Sums of the numbers of first events for the single components do not add up to the numbers of events in the composite endpoint.

Figure 1 – Time to first occurrence of kidney failure, sustained decline in eGFR ≥40% from baseline, or renal death in the FIDELIO-DKD study

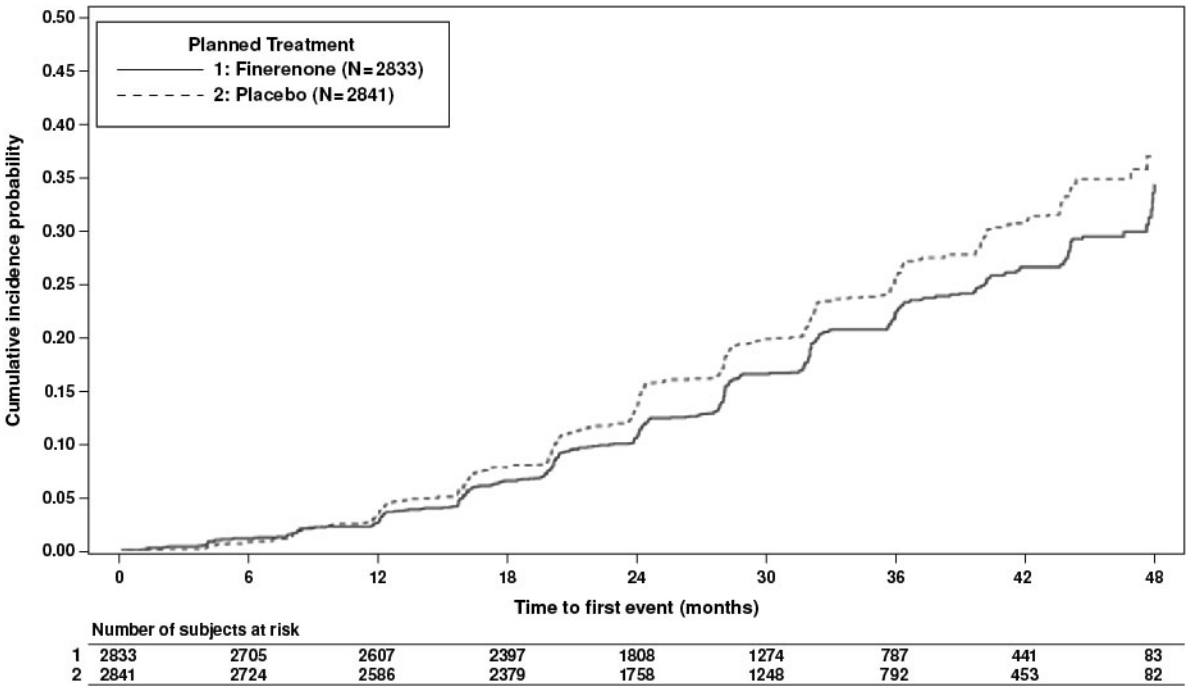
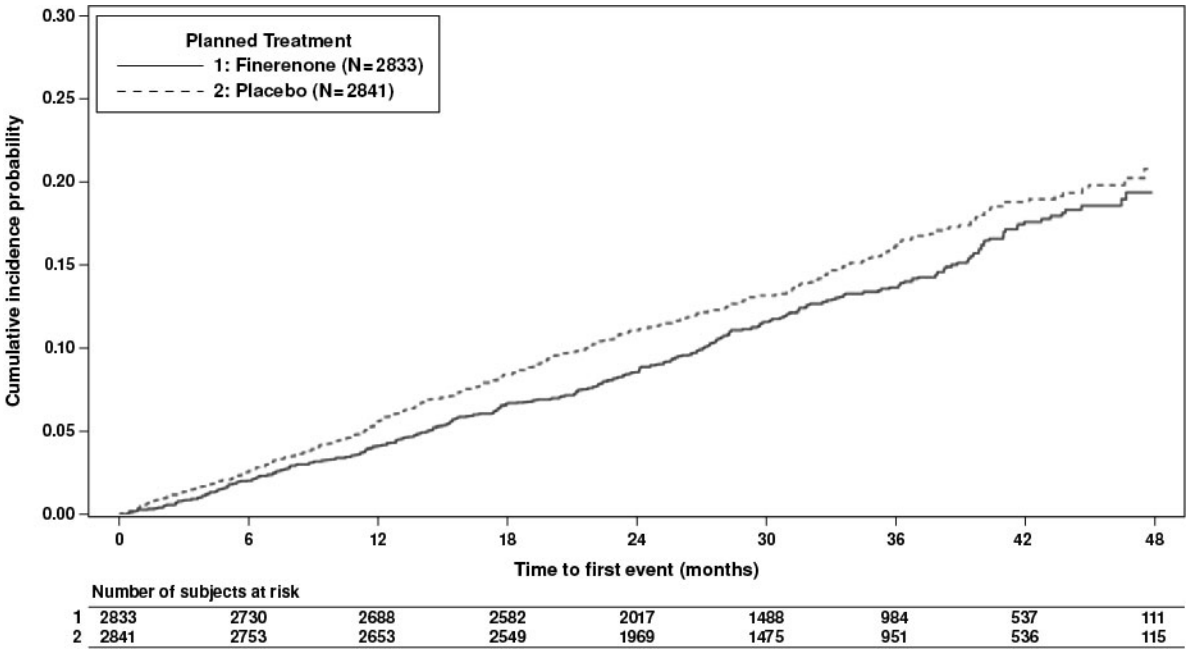


Figure 2 – Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure in the FIDELIO-DKD study



FIGARO-DKD STUDY

KERENDIA significantly reduced the risk of the primary composite endpoint of time CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure compared to placebo in a time to event analysis using the Cox proportional hazards model and log rank test (HR 0.87, 95% CI 0.76-0.98, p=0.0264). See Figure 3 and Table 11. The treatment effect for the primary endpoint was consistent across subgroups and was mainly driven by an effect on hospitalization for heart failure, though CV death also contributed to the treatment effect. A lower incidence rate of the secondary composite outcome of kidney failure, sustained eGFR decline of 40% or more or renal death was observed in the KERENDIA group compared to placebo, however this difference did not achieve statistical significance (HR 0.87, 95% CI 0.76-1.01, p=0.0689). See Table 11 and Figure 4.

Table 11 – Analysis of the primary and secondary time-to-event endpoints (and their individual components) in phase III study FIGARO-DKD

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	KERENDIA* 10 or 20 mg OD N=3686		**Placebo* N=3666**		**Treatment Effect KERENDIA / Placebo**	
Primary and Secondary Time- to-event Endpoints:	**n (%)**	**Event Rate (100 pt -yr)**	**n (%)**	**Event Rate (100 pt-yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure	458 (12.4%)	3.87	519 (14.2%)	4.45	0.87 [0.76; 0.98]	0.0264
• CV death	194 (5.3%)	1.56	214 (5.8%)	1.74	0.90 [0.74; 1.09]	-
• Non-fatal MI	103 (2.8%)	0.85	102 (2.8%)	0.85	0.99 [0.76; 1.31]	-
• Non-fatal stroke	108 (2.9%)	0.89	111 (3.0%)	0.92	0.97 [0.74; 1.26]	-
• Hospitalization for heart failure	117 (3.2%)	0.96	163 (4.4%)	1.36	0.71 [0.56; 0.90]	-
Secondary composite of kidney failure, sustained eGFR decline ≥40% or renal death	350 (9.5%)	3.15	395 (10.8%)	3.58	0.87 [0.76; 1.01]	0.0689**
• Kidney failure	46 (1.2%)	0.40	62 (1.7%)	0.54	0.72 [0.49; 1.05]	-

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	KERENDIA* 10 or 20 mg OD N=3686		Placebo* N=3666		Treatment Effect KERENDIA / Placebo	
• Sustained eGFR decline ≥ 40%	338 (9.2%)	3.04	385 (10.5%)	3.49	0.87 [0.75; >1.00]	-
• Renal death	0	-	2 (<0.1%)	-	-	-

* Treatment in addition to maximum tolerated labeled doses of ACEi or ARB.

** Not significant

p-value: two-sided p-value from stratified logrank test

CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, N = number of subjects, n = number of subjects with event, pt-yr = patient year.

Note: Time to first event was analyzed in a stratified Cox proportional hazards model. For patients with multiple events, only the first event contributed to the composite endpoint. Sums of the numbers of first events for the single components do not add up to the numbers of events in the composite endpoint.

Figure 3 – Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure in the FIGARO-DKD study

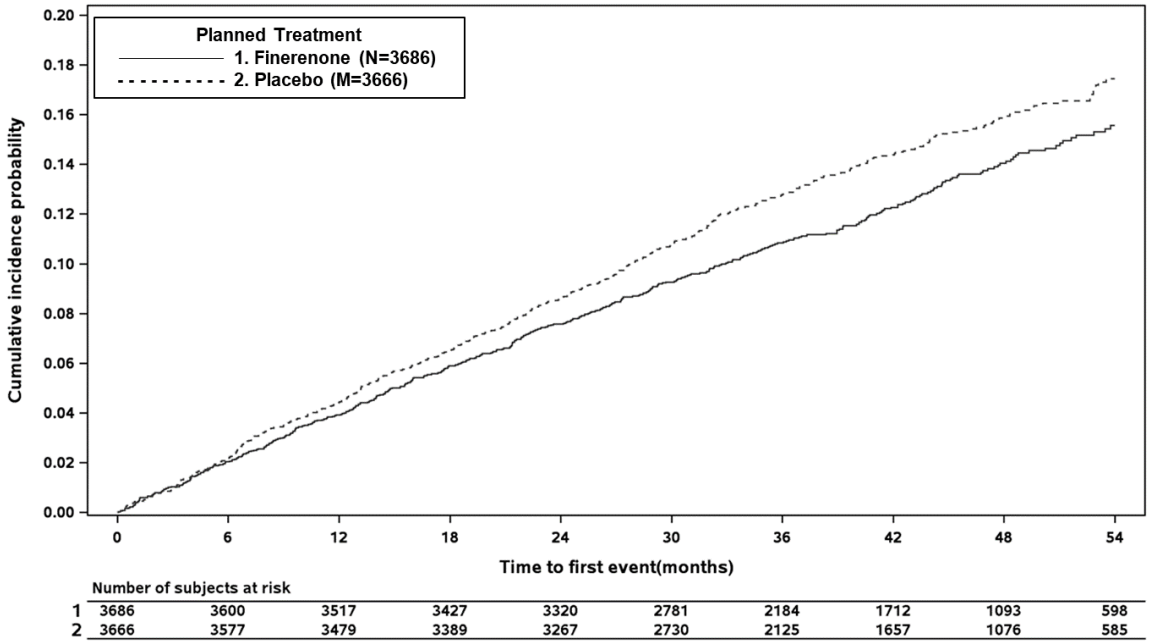
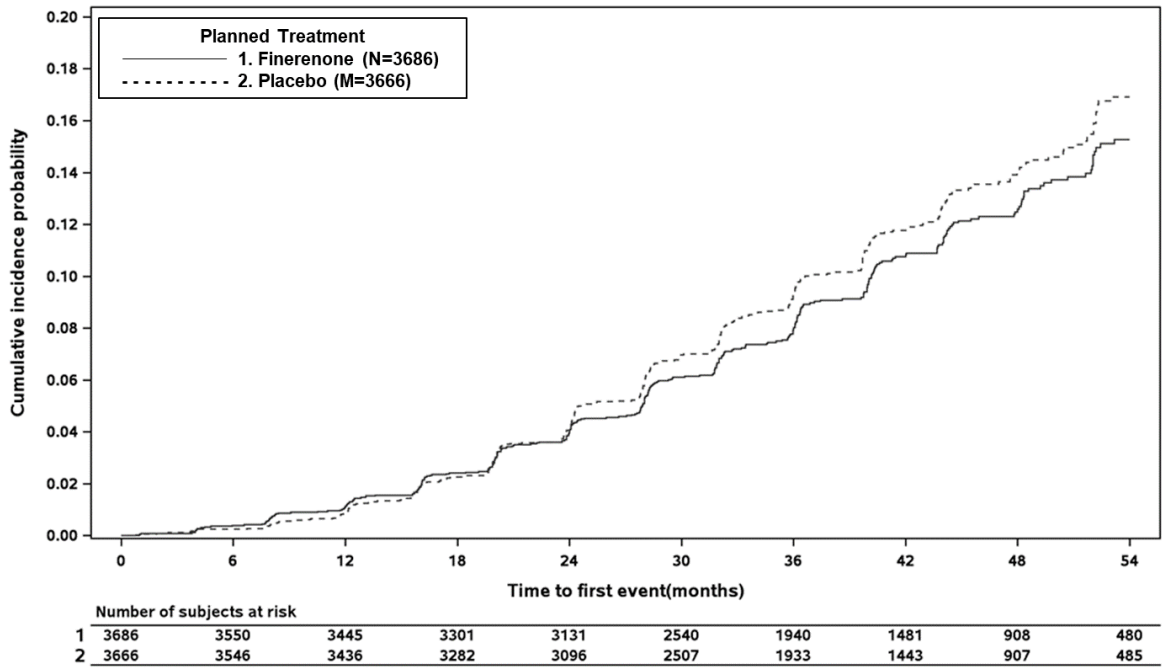


Figure 4 – Time to first occurrence of kidney failure, sustained decline in eGFR >40% from baseline, or renal death in the FIGARO-DKD study



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, genotoxicity, phototoxicity, carcinogenicity and male and female fertility.

Effects observed in repeat-dose toxicity studies were mainly due to exaggerated pharmacodynamic activities of finerenone and secondary adaptive responses.

In studies on embryo-fetal development, effects in rats were observed at exposures about 19 to 25 times those expected in humans, thereby indicating a reduced concern. In the pre- and post-natal developmental study, adverse effects (pup mortality, low body weight and pinna unfolding delays) were found in pups. In addition, increased locomotor activity in the offspring was observed, which may result from exposure during pregnancy.

Repeated Dose Toxicity

In the rat 26-week study, finerenone caused slight changes in electrolytes as well as slight to moderate changes in the adrenals. These findings are related to the mode of action. Adverse effects were seen at an $AUC_{unbound}$ of about 17 times that in humans (reduced body weight). The dose free of any adverse findings provided a safety margin of at least 6.

In the 4- and 13-week studies, rats showed mild degenerative changes in the kidney as well as mild changes in the urinary bladder, which were not reproduced in the chronic study. The high dose with

signs of general toxicity also caused atrophic changes in female genital organs. The $AUC_{unbound}$ in females at the high dose was about 21 times the human exposure.

In the chronic study in dogs, finerenone caused mild changes in the adrenal glands, which are regarded as mode-of-action-related. In addition, a decrease in prostate weights and size was found starting at an $AUC_{unbound}$ of 10 times the maximum human therapeutic exposure. There were no additional findings in the male genital tract at the high dose representing 60 times the maximum human exposure.

Carcinogenicity

In 2-year carcinogenicity studies, finerenone did not show a carcinogenic potential in male and female rats as well as female mice at doses representing 19 to 28 times the $AUC_{unbound}$ in humans. In male mice, finerenone resulted in an increase in Leydig cell adenoma at doses representing 26 times the $AUC_{unbound}$ in humans. A dose representing 17 times the $AUC_{unbound}$ in humans did not cause any tumors. Based on the known sensitivity of rodents to develop these tumors and the pharmacology-based mechanism at supratherapeutic doses as well as adequate safety margins, the increase in Leydig cell tumors in male mice is not considered clinically relevant.

Genotoxicity

Finerenone was non-genotoxic in an *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* chromosomal aberration assay in cultured Chinese hamster V79 cells, or the *in vivo* micronucleus assay in mice.

Reproductive and Developmental Toxicology

Male fertility in rats was not affected by KERENDIA at levels up to 16 times the human $AUC_{unbound}$ (see 7 WARNINGS AND PRECAUTIONS).

Finerenone caused reduced female fertility (decreased number of corpora lutea and implantation sites) as well as signs of early embryonic toxicity (increased post-implantational loss and decreased number of viable fetuses) at about 21 times the human $AUC_{unbound}$. In addition, reduced ovarian weights were found at about 17 times the human $AUC_{unbound}$. No effects on female fertility and early embryonic development were found at 10 times the human $AUC_{unbound}$. Additional animal studies demonstrated placental transfer of finerenone and/or its metabolites in pregnant rats (see 7 WARNINGS AND PRECAUTIONS).

In the embryo-fetal toxicity in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for $AUC_{unbound}$ (see 7 WARNINGS AND PRECAUTIONS).

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$. The increased locomotor activity in offspring may indicate a potential risk for the fetus. In

addition, because of the findings in pups, a risk for the nursing infant cannot be excluded (see 7 WARNINGS AND PRECAUTIONS and 7.1 Special populations).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrKERENDIA®

Finerenone Tablets

Read this carefully before you start taking **KERENDIA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KERENDIA**.

What is KERENDIA used for?

KERENDIA is used along with other medicines to treat adults with chronic kidney disease and type 2 diabetes to:

- slow the worsening of kidney damage
- lower the risk of dying from heart or blood vessel disease, having a heart attack, and being hospitalized for heart failure

How does KERENDIA work?

Your body makes a substance called aldosterone. Aldosterone is important to control blood pressure by acting on the kidney and the heart. Sometimes high levels of aldosterone may worsen your kidney and heart function. KERENDIA works by stopping the action of aldosterone and can help prevent damage to your kidneys and heart.

What are the ingredients in KERENDIA?

Medicinal ingredients: finerenone

Non-medicinal ingredients: cellulose microcrystalline, croscarmellose sodium, ferric oxide red (KERENDIA 10 mg film-coated tablet), ferric oxide yellow (KERENDIA 20 mg film-coated tablet), hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide

KERENDIA comes in the following dosage forms:

Tablet (film-coated): 10 mg and 20 mg

Do not use KERENDIA if:

- you are allergic to finerenone or any of the other ingredients of this medicine. KERENDIA tablets contain lactose.
- you are taking any medicines known as ‘strong CYP3A4 inhibitors’. Examples include:
  - itraconazole or ketoconazole – used to treat infections caused by a fungus or yeast
  - ritonavir, nelfinavir, or cobicistat – used to treat HIV infection
  - clarithromycin – used to treat bacterial infections
  - telithromycin – used to treat pneumonia

- nefazodone – used to treat depression
- you have Addison's disease

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KERENDIA. Talk about any health conditions or problems you may have, including if you:

- have or have had a high level of potassium in your blood (hyperkalemia)
- have severe loss of kidney function (severe renal impairment) or end-stage renal disease (kidney failure)
- have moderate or severe liver damage (moderate or severe hepatic impairment or Child Pugh B or C)
- have one of the following rare hereditary diseases, because KERENDIA contains lactose:
  - galactose intolerance
  - Lapp lactase deficiency
  - glucose-galactose malabsorption
- are pregnant, think you are pregnant, or are planning to become pregnant
- are breastfeeding or are planning to breastfeed. You should not breastfeed while taking KERENDIA

Other warnings you should know about:

Pregnancy: KERENDIA may harm your unborn baby. If you become pregnant while taking KERENDIA, tell your healthcare professional **right away**. KERENDIA should not be taken during pregnancy unless you and your healthcare professional have decided you should. If you are of child-bearing potential, use a reliable method of birth control.

Check-Ups: During treatment with KERENDIA, your healthcare professional will perform regular blood tests to monitor:

- your potassium levels
- your kidney function

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take KERENDIA if you:

- are taking medicines known as 'strong CYP3A4 inhibitors'. These medicines **strongly decrease** the activity of a class of enzymes in your body, called 'CYP3A4 enzymes'. Examples include:
  - itraconazole or ketoconazole – used to treat infections caused by a fungus or yeast
  - ritonavir, nelfinavir, or cobicistat – used to treat HIV infection
  - clarithromycin – used to treat bacterial infections
  - telithromycin – used to treat pneumonia
  - nefazodone – used to treat depression

The following may interact with KERENDIA:

- Medicines known as 'weak or moderate CYP3A4 inhibitors'. These medicines **decrease** the activity of a class of enzymes in your body, called 'CYP3A4 enzymes'. Examples include:
  - erythromycin – used to prevent and treat bacterial infections
  - verapamil – used to treat high blood pressure, chest pain, and fast heartbeat
  - fluvoxamine – used to treat depression and 'obsessive-compulsive disorder (OCD)'

  If you take KERENDIA while taking any of these medicines, you may get too much of the active substance, finerenone, in your blood. You may have more side effects.
- Medicines known as 'moderate or strong CYP3A4 inducers'. These medicines **increase** the activity of a class of enzymes in your body, called 'CYP3A4 enzymes'. Examples include:
  - rifampicin – used to treat bacterial infections
  - carbamazepine, phenytoin, or phenobarbital – used to treat seizures
  - St. John's Wort – a herbal product used to treat depression
  - Efavirenz – used to treat HIV infection

  If you take KERENDIA while taking any of these medicines, you may not get enough of the active substance, finerenone, in your blood. KERENDIA may not work as expected.
- Medicines that may increase the level of potassium in your blood. Examples include:
  - 'water pills' that remove excess water from your body in urine (potassium-sparing diuretics), such as amiloride or triamterene
  - other medicines like finerenone, such as eplerenone or spironolactone
  - trimethoprim, or a combination of trimethoprim and sulfamethoxazole, to treat bacterial infections
  - potassium supplements

  If you take KERENDIA while taking any of these medicines, you may get too much potassium in your blood (hyperkalemia). This may be unsafe for you.
- Grapefruit or grapefruit juice.

How to take KERENDIA:

- Always take KERENDIA exactly as your healthcare professional has told you.
- Try to take KERENDIA at the same time every day.
- You can take KERENDIA with a glass of water, with or without food. However, do not eat grapefruit or drink grapefruit juice while taking KERENDIA.
- If you cannot swallow the whole tablet, you can crush it. Mix it with water or soft foods, such as applesauce, and take it right away.

Usual dose:

The usual dose is 1 tablet once daily.

Your healthcare professional will decide the best dose for you. After 4 weeks of treatment, your healthcare professional will perform blood tests to see how your body is responding to and tolerating KERENDIA. Depending on the results, your doctor may increase, decrease, or continue with the same dose.

Overdose:

If you think you, or a person you are caring for, have taken too much KERENDIA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Do not take 2 tablets on the same day to make up for a missed dose. If you forget to take your dose and it is still the same day, take the tablet as soon as you remember. If it is the next day, skip the missed dose and take your next dose as scheduled.

What are possible side effects from using KERENDIA?

These are not all the possible side effects you may have when taking KERENDIA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Itchy skin

Serious side effects and what to do about them			
Symptom / Effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hyperkalemia (high level of potassium in the blood): weakness or tiredness, feeling sick (nausea), numbness in the hands and lips, muscle cramps, decreased pulse rate		✓	
COMMON			
Anemia (decreased number of red blood cells): looking-pale, weakness, tiredness, loss of energy, lightheadedness, shortness of breath, unusually fast heartbeat, chest pain		✓	
Decrease in how well the kidneys work: urinating more or less often than usual, fatigue, muscle cramps, feeling sick (nausea) or vomiting, loss of appetite		✓	
Hyperuricemia (high level of uric acid in the blood): pain, stiffness and/or swelling and redness in the joints		✓	
Hyponatremia (low level of sodium in the blood): feeling sick (nausea), tiredness, headache, confusion, muscle weakness, spasms or cramps		✓	
Hypotension (low blood pressure): dizziness, lightheadedness, fainting, blurred vision, feeling sick (nausea), vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store bottles or blisters at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date stated on the product labels.
- Do NOT throw away any medicines in the garbage, down the sink or in the toilet. Ask your pharmacist how to throw away expired or unused KERENDIA. These measures will help protect the environment.
- Keep out of sight and reach of children.

If you want more information about KERENDIA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

This leaflet was prepared by

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