▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
Kerendia® (finerenone) film-coated tablets

1 NAME OF THE MEDICINE

finerenone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KERENDIA 10mg film-coated tablet contains 10 mg finerenone
KERENDIA 20mg film-coated tablet contains 20 mg finerenone

KERENDIA contains lactose monohydrate

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

- KERENDIA 10 mg film-coated tablet

Pink, oval-oblong tablet with a length of 10 mm and a width of 5 mm, marked ´10´ on one side and ´FI´ on the other side

- KERENDIA 20 mg film-coated tablet

Yellow, oval-oblong tablet with a length of 10 mm and a width of 5 mm, marked ´20´ on one side and ´FI´ on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KERENDIA is indicated to delay progressive decline of kidney function in adults with chronic kidney disease associated with Type 2 diabetes (with albuminuria), in addition to standard of care (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

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 '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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

If serum potassium > 5.0 mmol/L, initiation of KERENDIA treatment is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

- 20 mg once daily if eGFR ≥ 60 mL/min/1.73m^2
- 10 mg once daily if eGFR ≥ 25 to < 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, re-measure 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 Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 1: Continuation of KERENDIA treatment and dose adjustment

Serum potassium (mmol/L)	Finerenone dose after 4 weeks
≤ 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.
4.9 – 5.5	Maintain dose.
> 5.5	Withhold finerenone. Restart at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.

Method of administration

Oral use.

Tablets may be taken with a glass of water and with or without food (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Avoid taking KERENDIA with grapefruit or grapefruit juice (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

For patients who are unable to swallow whole tablets, KERENDIA tablet may be crushed and mixed with water or soft foods, such as apple sauce, immediately prior to use and administered orally (see Section 5.2 PHARMACOKINETIC PROPERTIES).

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.

The maximum daily dose of KERENDIA is 20 mg.

Patients with hepatic impairment

In patients with severe hepatic impairment (Child Pugh C), avoid treatment with KERENDIA (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES). In patients with mild or moderate hepatic impairment, no initial dose adjustment is required (Child Pugh A or B) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

In patients with moderate hepatic impairment (Child Pugh B), consider additional serum potassium monitoring and adapt monitoring according to patient characteristics (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Patients with renal impairment

Initiation of KERENDIA treatment

In patients with eGFR ≥ 25 to < 60 mL/min/1.73m^2, the starting dose of KERENDIA is 10 mg once daily. See section 'Initiation of treatment.'

In patients with eGFR < 25 mL/min/1.73m^2, initiation of KERENDIA treatment is not recommended as clinical experience is limited (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

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 up-titration. See Table 1 and section 'Continuation of treatment.'

In patients with end-stage renal disease (eGFR < 15 mL/min/1.73m^2), continue KERENDIA treatment with caution regarding serum potassium levels as clinical experience is limited (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients taking concomitant medications

In patients taking Kerendia concomitantly with moderate or weak 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Elderly patients

No dose adjustment is required in the elderly (see Section 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Finerenone is contraindicated in patients:

- taking concomitant medications that are strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) (see Section 'Interaction with other medicinal products and other forms of interaction').
- with adrenal insufficiency.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperkalaemia

Hyperkalaemia has been observed in patients treated with KERENDIA.
Some patients are at a higher risk to develop hyperkalaemia. Risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalaemia. Consider more frequent monitoring in these patients.
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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
Withhold KERENDIA in treated patients if serum potassium > 5.5 mmol/L. Follow local guidelines for the management of hyperkalaemia. Restart KERENDIA at 10 mg once daily if serum potassium ≤ 5.0 mmol/L (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Re-measure 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Concomitant medications

The risk of hyperkalaemia also may increase with the intake of concomitant medications that may increase serum potassium (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). See also 'Concomitant use of substances that affect finerenone exposure.'
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.

Use in Hepatic Impairment

Patients with severe hepatic impairment (Child Pugh C) have not been studied (see Section 5.2 PHARMACOKINETIC PROPERTIES). Due to an expected significant increase in finerenone exposure, avoid use of KERENDIA in patients with severe hepatic impairment (see Section 4.2 DOSE AND METHOD OF 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in Renal Impairment

The risk of hyperkalaemia increases with decreasing renal function. Ongoing monitoring of renal function should be performed as needed according to standard practice (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
Initiation of KERENDIA treatment is not recommended in patients with eGFR < 25 mL/min/1.73m^2 as clinical experience is limited (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).
Continue KERENDIA treatment with caution regarding serum potassium levels in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) as clinical experience is limited (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the Elderly

No dose adjustment is required in the elderly (See Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric Use

The safety and efficacy of KERENDIA have not been established in patients under 18 years of age. Therefore, KERENDIA is not recommended for use in paediatric patients.

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS); Table 4: Laboratory test abnormalities reported in ≥ 1% of Kerendia-treated patients in the phase III study FIDELIO-DKD, Table 2: Adverse reactions reported with KERENDIA in the phase III study FIDELIO-DKD and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

Embryo-foetal toxicity

Animal data have shown reproductive toxicity. The relevance for humans is unknown. KERENDIA should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the foetus. If the patient becomes pregnant while taking KERENDIA, the patient should be informed of potential risks to the foetus. Advise women of childbearing potential to use effective contraception during treatment with KERENDIA. Advise women not to breastfeed during treatment with KERENDIA (See Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Concomitant use of substances that affect finerenone exposure

- ***Moderate and weak CYP3A4 inhibitors***

The concomitant use of KERENDIA with moderate CYP3A4 inhibitors (e.g., erythromycin and verapamil) and weak CYP3A4 inhibitors (e.g., amiodarone and fluvoxamine) is expected to increase finerenone exposure (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Monitor serum potassium especially during initiation of or changes to dosing of KERENDIA or the CYP3A4 inhibitor (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

- ***Strong and moderate CYP3A4 inducers***

Avoid concomitant use of KERENDIA with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) or moderate CYP3A4 inducers (e.g., efavirenz), which are expected to markedly decrease finerenone plasma concentrations and result in reduced therapeutic effect (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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%]). Accordingly, agents that affect CYP3A4 may significantly alter exposure to finerenone.

Effect of CYP3A4 inhibitors on finerenone

- ***Strong CYP3A4 inhibitors***

Simulations suggest that concomitant use of KERENDIA with itraconazole (200 mg BID), a strong CYP3A4 inhibitor, increases finerenone AUC (+531%) and C_{max} (+137%). Clarithromycin (500 mg BID), another strong inhibitor, also is predicted to increase finerenone AUC (+428%) and C_{max} (+125%). 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 Section 4.3 CONTRAINDICATIONS).

- ***Moderate CYP3A4 inhibitors***

Concomitant use of erythromycin (500 mg thrice daily), a moderate CYP3A4 inhibitor, increased finerenone mean AUC and C_{max} by 248% and 88%, respectively. Another moderate CYP3A4 inhibitor, verapamil (240 mg controlled-release tablet once daily), increased finerenone mean AUC and C_{max} by 170% and 120%, respectively. Serum potassium may increase, and therefore, monitoring of serum potassium is recommended *(*see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).*

- ***Weak CYP3A4 inhibitors***

In an analysis of KERENDIA in patients, the use of amiodarone, a weak CYP3A4 inhibitor, was estimated to result in a 21% increase of finerenone AUC. Simulations suggest that fluvoxamine (100 mg BID), another weak inhibitor, increases finerenone AUC (+57%) and C_{max} (+38%). Serum potassium may increase, and therefore, monitoring of serum potassium is recommended (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- ***Grapefruit***

Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentration of finerenone and should be avoided (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Effect of strong and moderate CYP3A4 inducers on finerenone

Simulations suggest that rifampicin (600 mg OD), a strong CYP3A4 inducer, decreases finerenone AUC (-93%) and C_{max} (-86%). Efavirenz (600 mg OD), a moderate CYP3A4 inducer, is predicted to decrease finerenone AUC (-81%) and C_{max} (-68%).
Concomitant use of KERENDIA with rifampicin and other strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, St John's Wort) or with efavirenz and other moderate CYP3A4 inducers, markedly decreases finerenone plasma concentration and results in reduced therapeutic effect and should be avoided (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- ***Lack of clinically relevant drug-drug interaction***

Concomitant use of gemfibrozil (600 mg twice daily), a strong inhibitor of CYP2C8, increased finerenone mean AUC and C_{max} by 10% and 16%, respectively. This is not clinically relevant.

Pre- and co-treatment with the proton pump inhibitor omeprazole (40 mg once daily) had no effect on finerenone mean AUC and mean C_{max}.

Concomitant use of antacid aluminium hydroxide and magnesium hydroxide (70 mVal) had no effect on finerenone mean AUC and reduced its mean C_{max} by 19%. This is not clinically relevant.

Effect of finerenone on other substances

In vivo a multiple-dose regimen of 20 mg finerenone once-daily had no effect on the AUC of the CYP3A4 probe substrate midazolam. Finerenone neither inhibits nor induces CYP3A4 in patients at therapeutic doses.
A single dose of 20 mg finerenone also had no effect on AUC and C_{max} of the CYP2C8 probe substrate repaglinide. Finerenone does not inhibit CYP2C8 in patients at therapeutic doses.
Lack of mutual pharmacokinetic interaction was demonstrated between finerenone and the CYP2C9 substrate warfarin and between finerenone and the P-gp substrate digoxin.

Pharmacodynamic interactions

- ***Medications that increase serum potassium***

Medications that increase serum potassium

It is anticipated that medications that increase serum potassium will increase the risk of hyperkalaemia 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.

(See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No human data on the effect of KERENDIA on fertility are available. No effect on male fertility was observed with finerenone in rats at oral doses up to 30 mg/kg/day (estimated to yield 16 times the exposure in patients at the maximum recommended human dose of 20 mg/day [based on plasma AUC for unbound drug]). In female rats, inhibition of ovulation was seen with treatment at 30 mg/kg/day (yielding 21 times the clinical exposure), while no effect on female fertility was observed at 3 mg/kg/day (relative exposure, 10). Based on these animal data and the margin of exposure, impairment of male and female fertility is not expected in patients.

Use in Pregnancy (Category D)

There are no data on the use of KERENDIA in pregnant women.

Adverse effects on embryofetal development, including teratogenicity, were observed with finerenone in animals. Placental transfer of finerenone and/or its metabolites was demonstrated in the rat.
Administration of finerenone to pregnant rats reduced fetal weight and impaired fetal ossification at oral doses ≥10 mg/kg/day. Increased external and skeletal variations (slight oedema, shortened umbilical cord and slightly enlarged fontanelle) and malformation of the aortic arch were observed at 30 mg/kg/day. These doses yield exposure 19–25 times higher than in patients at the maximum recommended human dose of 20 mg/day (based on plasma AUC for unbound drug), and were maternotoxic. Maternal dosing with finerenone at ≥3 mg/kg/day during gestation and lactation (relative exposure, 4), decreased birth weight, increased perinatal mortality and slightly increased locomotor activity of rat pups. At 10 mg/kg/day, postnatal body weight gain was reduced and development delayed. The observed effect on neurobehaviour is consistent with a pharmacologically-mediated antidepressant-like effect of finerenone as a result of exposure in the fetal brain in utero. No adverse effects on embryofetal development were observed with finerenone in rabbits up to the highest dose tested (2.5 mg/kg/day, yielding 13 times the clinical exposure).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- ***Women of childbearing potential / Contraception***

KERENDIA may cause embryofetal harm when administered during pregnancy. Women of childbearing potential should use effective contraception during treatment with KERENDIA (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in Lactation

It is unknown whether finerenone or its metabolites are excreted in human breast milk. Excretion of finerenone and its metabolites in milk was shown in rats. Rat pups exposed to finerenone *in utero* and through consumption of maternal milk showed adverse effects (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION). A risk to the nursing infant cannot be excluded. Breastfeeding should be discontinued if use of KERENDIA is considered essential (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of KERENDIA in patients with chronic kidney disease and type 2 diabetes was evaluated in the pivotal phase III study FIDELIO-DKD. In this study, 2,827 patients received KERENDIA (10 or 20 mg once daily) and 2,831 received placebo. For patients in the KERENDIA group, the mean duration of treatment was 2.2 years.
The most frequently reported (≥ 10%) adverse reaction was hyperkalaemia. See 'Description of selected adverse reactions' below (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Tabulated list of adverse reactions

The adverse reactions reported with KERENDIA are summarised in Table 2 below by MedDRA system organ class and by frequency.
Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using the following convention:

very common (≥1/10)
common (≥1/100 to <1/10)
uncommon (≥1/1,000 to <1/100)
rare (≥1/10,000 to <1/1,000)
very rare (<1/10,000)

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2: Adverse reactions reported with KERENDIA in the phase III study FIDELIO-DKD

MedDRA System Organ Class	Very common	Common
Metabolism and nutrition disorders	Hyperkalaemia[1]	Hyponatremia[2]
Vascular disorders		Hypotension[3, 4]
Investigations		Glomerular filtration rate decreased[5]

[1] includes Blood potassium increased and Hyperkalaemia
[2] includes Blood sodium decreased and Hyponatremia
[3] includes Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension
[4] In patients treated with Kerendia, the mean systolic blood pressure (SBP) decreased by 3 mmHg and the mean diastolic blood pressure (DBP) decreased by 1-2 mmHg at month 1, remaining stable thereafter. The majority of hypotension events were mild or moderate and resolved. Events associated with hypotension, e.g., dizziness, syncope, or fall, were not more frequent in patients using Kerendia in comparison to placebo.
[5] An initial decrease in eGFR (mean 2 mL/min/1.73m^2) attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation.

Table 3: Adverse reactions reported in ≥1% of Kerendia treated patients in the phase III study FIDELIO-DKD

Adverse reactions	Kerendia N = 2827 n (%)	Placebo N = 2831 n (%)
Hyperkalaemia[1]	516 (18.3)	255 (9.0)
Hypotension[2,3]	135 (4.8)	96 (3.4)
Hyponatremia[4]	40 (1.4)	19 (0.7)

[1] includes Blood potassium increased and Hyperkalaemia
[2] includes Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension
[3] In patients treated with Kerendia, the mean systolic blood pressure (SBP) decreased by 3 mmHg and the mean diastolic blood pressure (DBP) decreased by 1-2 mmHg at month 1, remaining stable thereafter. The majority of hypotension events were mild or moderate and resolved. Events associated with hypotension, e.g., dizziness, syncope, or fall, were not more frequent in patients using Kerendia in comparison to placebo.
[4] includes Blood sodium decreased and Hyponatremia

Table 4: Laboratory test abnormalities reported in ≥ 1% of Kerendia-treated patients in the phase III study FIDELIO-DKD

Laboratory test Abnormalities	Kerendia N = 2827 n (%)	Placebo N = 2831 n (%)
Glomerular filtration rate decreased[1]	179 (6.3)	133 (4.7)

[1] An initial decrease in eGFR (mean 2 mL/min/1.73m2) attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation.

Description of selected adverse reactions

- ***Hyperkalaemia***

In the FIDELIO-DKD study, hyperkalaemia events were reported in 18.3% of KERENDIA -treated patients compared with 9.0% of placebo-treated patients. In patients treated with KERENDIA, the majority of hyperkalaemia events were mild to moderate. 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, with a maximum between-group difference of 0.23 mmol/L observed at Month 4, remaining stable thereafter. For specific recommendations, refer to Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

No cases of adverse events associated with finerenone overdose in humans have been reported. The most likely manifestation of overdose is anticipated to be hyperkalaemia. If hyperkalaemia develops, standard treatment should be initiated.
Finerenone is unlikely to be efficiently removed by haemodialysis given its fraction bound to plasma proteins of about 90%.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: C03DA05

Mechanism of Action

Finerenone is a nonsteroidal antagonist of the mineralocorticoid receptor (MR) that potently attenuates inflammation and fibrosis mediated by MR overactivation. The MR is expressed in the kidneys, heart and blood vessels where finerenone also counteracts sodium retention and hypertrophic processes. Finerenone has high selectivity for the MR due to its nonsteroidal structure and bulky binding mode. Finerenone has no relevant affinity for androgen, progesterone, estrogen and glucocorticoid receptors and therefore does not cause sex hormone-related adverse events (e.g., gynecomastia). Its binding to the MR leads to a specific receptor ligand complex that blocks recruitment of transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators.

- ***Effects in healthy participants***

Finerenone (multiple doses of 10 mg and 20 mg twice daily or 40 mg once daily over 10 days) had no consistent effect on natriuresis or urine potassium in healthy male participants. These regimens 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.

However, following activation of the MR with the MR agonist fludrocortisone (0.5 mg), finerenone (single doses of 2.5, 5, 10, 20 mg PEG solution or 20 mg tablets) showed dose dependent natriuretic effects in healthy male participants. Moreover, finerenone (at doses of 5 to 20 mg) significantly decreased urinary potassium excretion as compared to placebo.
Single or multiple doses of finerenone did not influence vital signs parameters in healthy participants.

- ***Cardiac electrophysiology***

In a thorough QT study in 57 healthy participants, there was no indication of a QT/QTc prolonging effect of finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic), indicating that finerenone has no effect on cardiac repolarization.

Clinical Trials

The FIDELIO-DKD study was a randomised, double-blind, placebo-controlled, multicentre Phase III study investigating the effect of KERENDIA compared to placebo on kidney and cardiovascular outcomes in adult patients with chronic kidney disease and type 2 diabetes. 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 labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

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 hospitalisation for heart failure.

The trial analysed 5,674 patients randomly assigned to receive either KERENDIA 10 mg or 20 mg once daily (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 enrolment 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 haemoglobin 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, almost all 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%).

KERENDIA significantly reduced the risk of the primary composite endpoint 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 Figure 1/Table 5 below. The key secondary endpoint results (composite of CV death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure) were favourable overall (HR (95% CI): 0.86 (0.75-0.99), p=0.0339), but with an indeterminate effect observed for the 'non-fatal stroke' component with a HR (95% CI): 1.027 (0.765-1.380). Prespecified secondary time-to-event endpoints are included in Table 5. For the secondary endpoint of change in UACR from baseline to month 4, a relative reduction of 31.2% was observed in the KERENDIA group compared to placebo. The treatment effect for the primary and key secondary endpoints was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure (BP) and HbA1c at baseline.

In the FIDELIO-DKD study, hyperkalaemia events were reported in 18.3% of KERENDIA-treated patients compared with 9.0% of placebo-treated patients. Hospitalisation due to hyperkalaemia for the KERENDIA group was 1.4% versus 0.3% in the placebo group. Hyperkalaemia leading to permanent discontinuation in patients who received KERENDIA was 2.3% versus 0.9% in the placebo group.

In the FIDELIO-DKD study, glomerular filtration rate decreased events were reported in 6.3% of KERENDIA -treated patients compared with 4.7% of placebo-treated patients, and those leading to permanent discontinuation in patients receiving KERENDIA were 0.2% versus 0.3% in the placebo group. Patients on KERENDIA experienced an initial decrease in eGFR (mean 2 mL/min/1.73m^2) that attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation. The initial decrease in eGFR was associated with long term preservation of kidney function.

Table 5: 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 hospitalisation 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]	-
Hospitalisation for heart failure	139 (4.9%)	1.89	162 (5.7%)	2.21	0.86 [0.68;1.08]	-
All-cause mortality	219 (7.7%)	2.90	244 (8.6%)	3.23	0.90 [0.75; 1.07]	0.2348**
All-cause hospitalisation	1263 (44.6%)	22.56	1321 (46.5%)	23.87	0.95 [0.88; 1.02]	-
Kidney failure, sustained eGFR decline ≥ 57% or renal death	252 (8.9%)	3.64	326 (11.5%)	4.74	0.76 [0.65; 0.90]	-

* Treatment in addition to maximum tolerated labeled doses of ACEi or ARB.
** Not significant

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

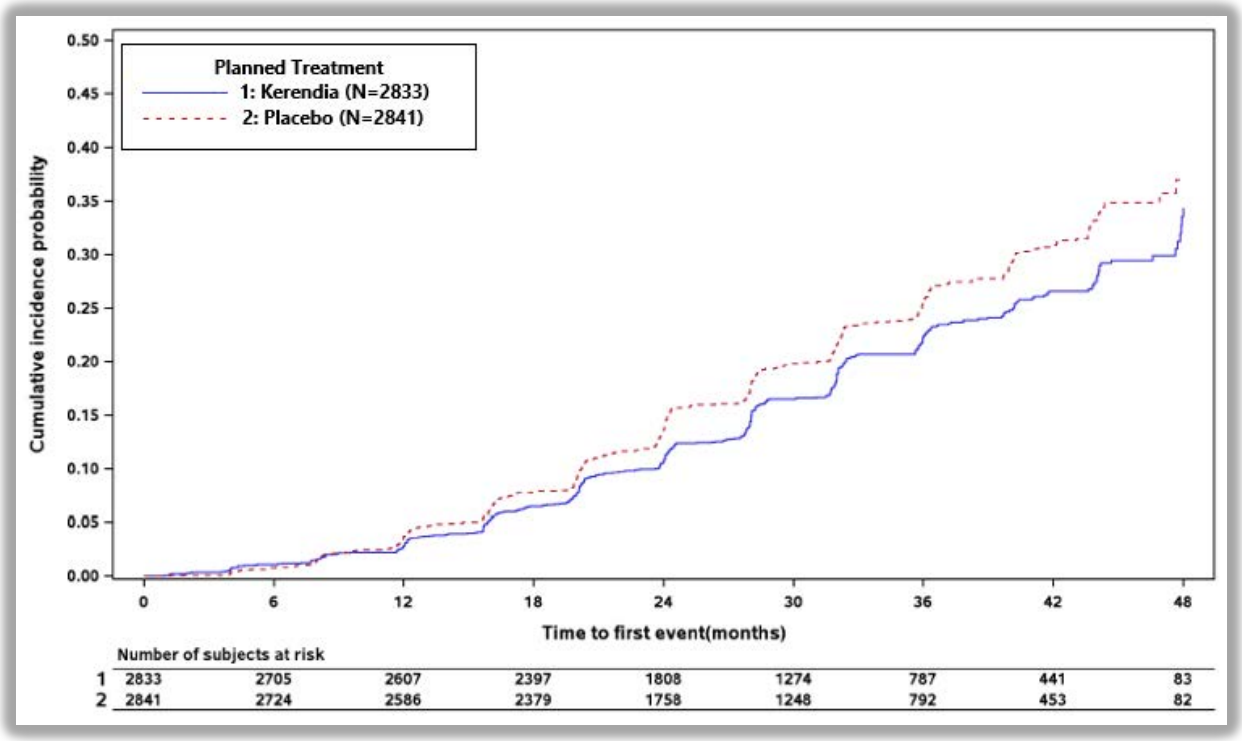
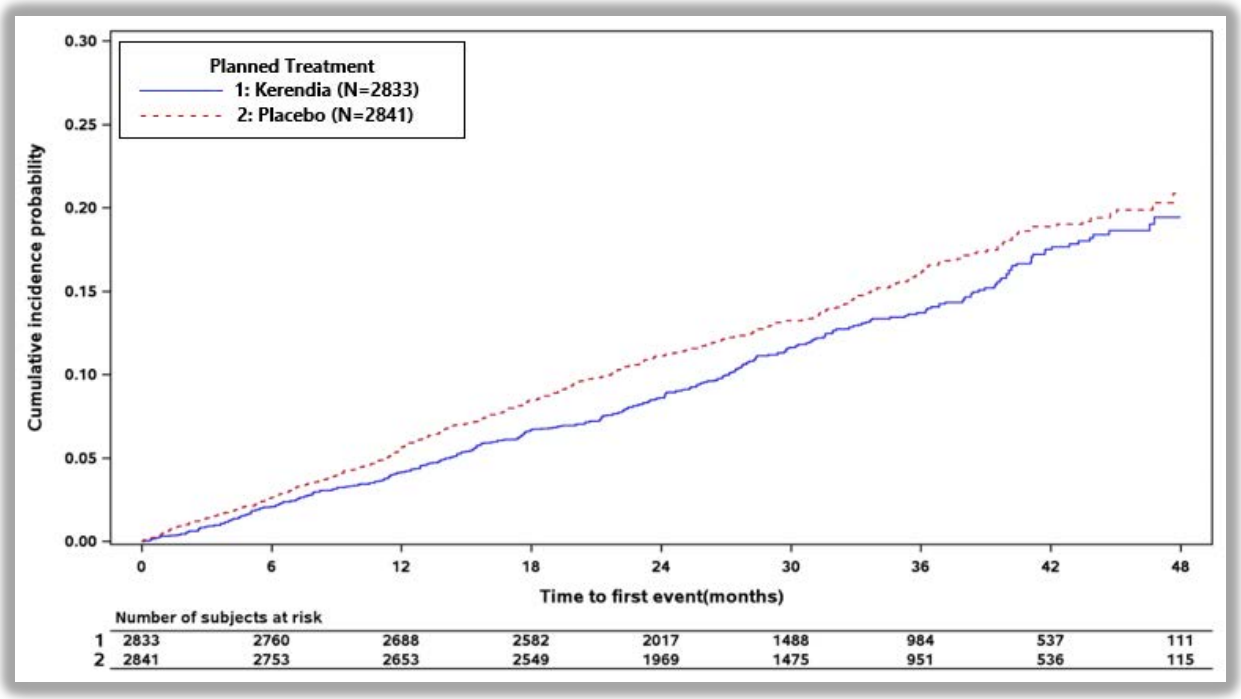


Figure 2: Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure in the FIDELIO-DKD study



5.2 PHARMACOKINETIC PROPERTIES

The concentration-effect relationship over time for UACR was characterised by a maximum effect model indicating saturation at high exposures. The model-predicted time to reach the full (99%) steady-state drug effect on UACR was 138 days. The pharmacokinetic (PK) half-life was 2-3 hours and PK steady state was achieved after 2 days, indicating timescale separation.

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 a substrate of the efflux transporter P-gp *in vivo*. Intake with high fat, high calorie food increased finerenone AUC by 21%, reduced C_{max} by 19% and prolonged the time to reach C_{max} to 2.5 hours. This is not clinically relevant. Therefore, finerenone can be taken with or without food (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Distribution

The volume of distribution at steady state (V_{ss}) 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.

Excretion

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 faeces). About 80% of the administered dose was excreted via urine and approximately 20% of the dose was excreted via faeces, almost exclusively in the form of metabolites. With a systemic blood clearance of about 25 L/h, finerenone can be classified as a low clearance drug.

Special populations

- ***Patients with renal impairment***

Mild renal impairment (CLCR 60 - < 90 mL/min) did not affect finerenone AUC and C_{max}. Compared to subjects with normal renal function (CLCR ≥ 90 mL/min), the effect of moderate (CLCR 30 - < 60 mL/min) or severe (CLCR < 30 mL/min) renal impairment on AUC of finerenone was similar with increases by 34-36%. Moderate or severe renal impairment had no effect on C_{max} (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
Due to the high plasma protein binding, finerenone is not expected to be dialyzable.

- ***Patients with hepatic impairment***

There was no change in finerenone exposure in cirrhotic subjects with mild hepatic impairment (Child Pugh A) (see Section 4.2 DOSE AND METHOD OF 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
There are no data in patients with severe hepatic impairment (Child Pugh C) (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- ***Elderly patients***

Of the 2827 patients who received KERENDIA in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients.
Elderly subjects (≥65 years of age) exhibited higher finerenone plasma concentrations than younger subjects (≤45 years of age), with mean AUC and C_{max} values being 34% and 51% higher in the elderly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Report No. R-13179 Population-pharmacokinetic analyses did not identify age as a covariate for finerenone AUC or C_{max}.

- ***Body Weight***

Population-pharmacokinetic analyses identified body weight as a covariate for finerenone C_{max}. The C_{max} of a subject with a body weight of 50 kg was estimated to be 43% to 51% higher compared to a subject of 100 kg. Dose adaptation based on body weight is not warranted (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Finerenone was non-genotoxic in assays for mutagenicity in bacteria and for chromosomal aberrations in vitro (in Chinese hamster V79 cells), and the mouse bone marrow micronucleus test.

Carcinogenicity

In 2-year carcinogenicity studies, finerenone did not increase tumour incidence in male or female rats at oral doses up to 20 and 10 mg/kg/day, or in female mice at oral doses up to 7.5 mg/kg/day (yielding exposure 19–28 times higher than in patients at the maximum recommended human dose of 20 mg/day, based on plasma AUC for unbound drug). In male mice, finerenone resulted in an increase in Leydig cell adenoma at 30 mg/kg/day, representing 26 times the $AUC_{unbound}$ in humans. No carcinogenicity was evident with treatment at 10 mg/kg/day, representing 17 times the $AUC_{unbound}$ in humans. Based on the known sensitivity of rodents to develop these tumours and the pharmacology-based mechanism at supratherapeutic doses as well as the margin of exposure, the increase in Leydig cell tumours observed in male mice is not considered to indicate a particular carcinogenic risk to patients treated with KERENDIA.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:

Croscarmellose sodium
Hypromellose 5 cP
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Tablet coating:

Hypromellose 5 cP
Talc
Titanium dioxide
Iron oxide yellow (for KERENDIA 20mg film-coated tablet)
Iron oxide red (for KERENDIA 10mg film-coated tablet)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

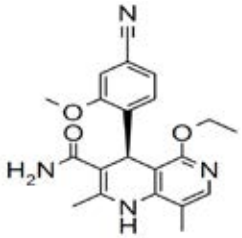
Container type: Alu/PVC/PVDC blister
Pack sizes: 14, 28, 98, 100
Some pack sizes may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



CAS Number: 1050477-31-0

Chemical name: 4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6 naphthyridine-3-carboxamide
Empirical formula: $C_{21}H_{22}N_4O_3$
Molecular weight: 378.43 g/mol

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Bayer Australia Limited
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875 Pacific Highway, Pymble NSW 2073
www.bayer.com.au

9 DATE OF FIRST APPROVAL

25 November 2021

10 DATE OF REVISION

Not applicable