

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kerendia 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Kerendia 40 mg film-coated tablets

Each film-coated tablet contains 40 mg of finerenone.

Excipient with known effect

Each film-coated tablet contains 25 mg of lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Kerendia 40 mg film-coated tablets

Grey-orange, oval-oblong film-coated tablet with a length of 11 mm and a width of 5 mm, marked '40' on one side and 'FI' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Kerendia is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) \geq 40% in adults.

4.2 Posology and method of administration

Posology

Heart failure with LVEF \geq 40%

The recommended target dose depends on renal function (eGFR) at initiation of finerenone treatment (see table 2):

- 40 mg once daily if eGFR \geq 60 mL/min/1.73 m²
- 20 mg once daily if eGFR \geq 25 to $<$ 60 mL/min/1.73 m²

The maximum recommended dose is 40 mg finerenone once daily.

Initiation of treatment

If serum potassium \leq 5.0 mmol/L, finerenone treatment can be initiated.

Serum potassium and estimated glomerular filtration rate (eGFR) have to be measured to determine if finerenone treatment can be initiated (see also section 4.4) and to determine the starting dose.

For monitoring of serum potassium, see below ‘Continuation of treatment.’

The recommended starting dose of finerenone is based on eGFR and is presented in table 1.

Table 1: Initiation of finerenone treatment and recommended dose

eGFR (mL/min/1.73 m²)	Starting dose (once daily)
\geq 60	20 mg
\geq 25 to $<$ 60	10 mg
$<$ 25	Not recommended

Continuation of treatment

Serum potassium and eGFR have to be remeasured 4 weeks after initiation or re-start of finerenone treatment or change in dose (see table 2 to determine continuation of finerenone treatment and dose adjustment).

Thereafter, serum potassium and eGFR have to be remeasured periodically and as needed based on patient characteristics.

See sections 4.4 and 4.5 for more information.

Table 2: Continuation of finerenone treatment and dose adjustment

		Current finerenone dose (once daily)		
		10 mg	20 mg	40 mg
Current serum potassium (mmol/L)	< 5.0	Increase to 20 mg finerenone once daily if eGFR has not decreased > 30% compared to the previous measurement	Increase to 40 mg once daily if eGFR has not decreased > 30% compared to the previous measurement Maintain 20 mg once daily if eGFR < 60 mL/min/1.73 m ² at initiation	Maintain 40 mg once daily Decrease to 20 mg once daily if eGFR has decreased > 30% compared to the previous measurement
	5.0 to < 5.5	Maintain 10 mg once daily	Maintain 20 mg once daily	Maintain 40 mg once daily Decrease to 20 mg once daily if eGFR has decreased > 30% compared to the previous measurement
	5.5 to < 6.0	Withhold finerenone Re-start at 10 mg once daily when serum potassium < 5.5 mmol/L.	Decrease to 10 mg once daily	Decrease to 20 mg once daily
	≥ 6.0	Withhold finerenone. Re-start at 10 mg once daily when serum potassium < 5.5 mmol/L or if repeatedly ≥ 5.5 mmol/L, wait to re-start until < 5.0 mmol/L.		

If eGFR decreases by $\geq 40\%$ compared to the previous measurement, consider reducing the dose or withholding finerenone. Once eGFR levels have stabilised, according to the individual patient's characteristics, consider increasing the dose or restarting treatment.

Missed dose

A missed dose should be taken as soon as the patient notices, but only on the same day.

The patient should not take 2 doses to make up for a missed dose.

Special populations

Elderly (≥ 65 years)

No dose adjustment is necessary in elderly patients (see section 5.2) but regular monitoring of renal function is recommended (see section 4.4).

Renal impairment

Initiation of treatment

In patients with eGFR < 25 mL/min/1.73 m², finerenone treatment should not be initiated due to limited clinical data (see sections 4.4 and 5.2).

Continuation of treatment

In patients with $\text{eGFR} \geq 15 \text{ mL/min/1.73 m}^2$, finerenone treatment can be continued with dose adjustment based on serum potassium. eGFR should be measured 4 weeks after initiation to determine whether the starting dose can be increased (see 'Posology and Continuation of treatment' table 2).

Due to limited clinical data, finerenone treatment should be discontinued in patients who have progressed to end-stage renal disease ($\text{eGFR} < 15 \text{ mL/min/1.73 m}^2$) (see section 4.4).

Hepatic impairment

Patients with

- severe hepatic impairment:
Finerenone should not be initiated (see sections 4.4 and 5.2). No data are available.
- moderate hepatic impairment:
No initial dose adjustment is required. Consider additional serum potassium monitoring and adapt monitoring according to patient characteristics (see sections 4.4 and 5.2).
- mild hepatic impairment:
No initial dose adjustment is required.

Concomitant use of other medicinal products

In patients taking finerenone concomitantly with moderate or weak CYP3A4 inhibitors, potassium supplements, trimethoprim, or trimethoprim/sulfamethoxazole, additional serum potassium monitoring and adaptation of monitoring according to patient characteristics should be considered (see section 4.4). Finerenone treatment decisions should be made as directed in table 2 (see 'Continuation of treatment').

Temporary discontinuation of finerenone may be necessary, when patients have to take trimethoprim, or trimethoprim/sulfamethoxazole. See sections 4.4 and 4.5 for more information.

Body weight

No dose adjustment is necessary based on body weight (see section 5.2).

Paediatric population

The safety and efficacy of finerenone in children and adolescents aged under 18 years have not yet been established. No data are available.

Method of administration

Oral use

Tablets may be taken with a glass of water and with or without food (see section 5.2). Tablets should not be taken with grapefruit or grapefruit juice (see section 4.5).

Crushing of tablets

For patients who are unable to swallow whole tablets, Kerendia tablets may be crushed and mixed with water or soft foods, such as apple sauce, directly before oral use (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant treatment with strong inhibitors of CYP3A4 (see section 4.5), e.g.,
 - itraconazole
 - ketoconazole
 - ritonavir
 - nelfinavir
 - cobicistat
 - clarithromycin
 - telithromycin
 - nefazodone
- Addison's disease

4.4 Special warnings and precautions for use

Hyperkalaemia

Hyperkalaemia has been observed in patients treated with finerenone (see section 4.8). Some patients are at a higher risk to develop hyperkalaemia.

Risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalaemia. In these patients more frequent monitoring has to be considered.

If serum potassium > 5.0 mmol/L, finerenone treatment should not be initiated.

Monitoring

Serum potassium and eGFR have to be remeasured 4 weeks after initiation, re-start or dose adjustment of finerenone. Thereafter, serum potassium has to be assessed periodically and as needed based on patient characteristics and serum potassium levels (see section 4.2).

Heart failure with LVEF \geq 40%

Initiation and continuation of treatment (see section 4.2)

If serum potassium \geq 6.0 mmol/L, finerenone treatment has to be withheld. Local guidelines for the management of hyperkalaemia have to be followed. Once serum potassium < 5.5 mmol/L, finerenone treatment can be restarted at 10 mg once daily. In case of repeated measurements of serum potassium \geq 5.5 mmol/L, finerenone treatment can only be restarted, when serum potassium is < 5.0 mmol/L.

Concomitant use of other medicinal products

The risk of hyperkalaemia also may increase with the intake of concomitant medicinal products that may increase serum potassium (see section 4.5). See also 'Concomitant use of substances that affect finerenone exposure'.

Finerenone should not be given concomitantly with

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

Finerenone should be used with caution and serum potassium should be monitored when taken concomitantly with

- potassium supplements or potassium-enriched salt substitutes.
- trimethoprim, or trimethoprim/sulfamethoxazole. Temporary discontinuation of finerenone may be necessary.

Worsening of renal function in patients with heart failure with LVEF \geq 40%

An increased incidence of worsening of renal function has been reported in patients with heart failure with LVEF \geq 40% treated with finerenone (see section 4.8).

Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR $<$ 60 mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently (see section 4.2).

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).

Initiation of treatment

Finerenone treatment should not be initiated in patients with eGFR $<$ 25 mL/min/1.73 m² as clinical data are limited (see sections 4.2 and 5.2).

Continuation of treatment

Due to limited clinical data, finerenone treatment should be discontinued in patients who have progressed to end-stage renal disease (eGFR $<$ 15 mL/min/1.73 m²).

Hepatic impairment

Finerenone treatment should not be initiated in patients with severe hepatic impairment (see section 4.2). These patients have not been studied (see section 5.2) but a significant increase in finerenone exposure is expected.

The use of finerenone in patients with moderate hepatic impairment may require additional monitoring due to an increase in finerenone exposure. Additional serum potassium monitoring and adaptation of monitoring have to be considered according to patient characteristics (see sections 4.2 and 5.2).

Patients with New York Heart Association (NYHA) class IV

Experience with finerenone in heart failure patients classified as NYHA class IV is limited (see section 5.1).

Elderly

Elderly are more likely to have impaired renal function and to be treated with medicinal products which may cause changes in renal function. Therefore, regular monitoring of renal function is recommended.

Concomitant use of substances that affect finerenone exposure

Moderate and weak CYP3A4 inhibitors

Serum potassium should be monitored during concomitant use of finerenone with moderate or weak CYP3A4 inhibitors (see sections 4.2 and 4.5).

Strong and moderate CYP3A4 inducers

Finerenone should not be used concomitantly with strong or moderate CYP3A4 inducers (see section 4.5).

Grapefruit

Grapefruit or grapefruit juice should not be consumed during finerenone treatment (see sections 4.2 and 4.5).

Embryo-foetal toxicity

Finerenone 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 a woman becomes pregnant while taking finerenone, she should be informed of potential risks to the foetus.

Women of childbearing potential should be advised to use effective contraception during treatment with finerenone.

Women should be advised not to breast-feed during treatment with finerenone.

See sections 4.6 and 5.3 for more information.

Information about excipients

Kerendia contains lactose

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

Kerendia contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Concomitant use contraindicated

Strong CYP3A4 inhibitors

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), since a marked increase in finerenone exposure is expected.

Concomitant use not recommended

Strong and moderate CYP3A4 inducers

Kerendia should not be used concomitantly with rifampicin and other strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, St John's Wort) or with efavirenz and other moderate CYP3A4 inducers. These CYP3A4 inducers are expected to markedly decrease finerenone plasma concentration and result in reduced therapeutic effect (see section 4.4).

Certain medicinal products that increase serum potassium

Kerendia should not be used concomitantly with potassium-sparing diuretics (e.g., amiloride, triamterene) and other MRAs (e.g., eplerenone, esaxerenone, spironolactone, canrenone). It is anticipated that these medicinal products increase the risk for hyperkalaemia (see section 4.4)

Grapefruit

Grapefruit or grapefruit juice should not be consumed during finerenone treatment, as it is expected to increase the plasma concentrations of finerenone through inhibition of CYP3A4 (see sections 4.2 and 4.4).

Concomitant use with precautions

Moderate CYP3A4 inhibitors

In a clinical study, concomitant use of erythromycin (500 mg three times a day) led to a 3.5-fold increase in finerenone AUC and 1.9-fold increase in its C_{max} . In another clinical study, verapamil (240 mg controlled-release tablet once daily) led to a 2.7- and 2.2-fold increase in finerenone AUC and C_{max} , respectively.

Serum potassium may increase, and therefore, monitoring of serum potassium is recommended, especially during initiation or changes to dosing of finerenone or the CYP3A4 inhibitor (see sections 4.2 and 4.4).

Weak CYP3A4 inhibitors

The physiologically based pharmacokinetic (PBPK) simulations suggest that fluvoxamine (100 mg twice daily), increases finerenone AUC (1.6-fold) and C_{max} (1.4-fold).

Serum potassium may increase, and therefore, monitoring of serum potassium is recommended, especially during initiation or changes to dosing of finerenone or the CYP3A4 inhibitor (see sections 4.2 and 4.4).

Certain medicinal products that increase serum potassium (see section 4.4)

Concomitant use of Kerendia with potassium supplements and trimethoprim, or trimethoprim/sulfamethoxazole is anticipated to increase the risk of hyperkalaemia. Monitoring of serum potassium is required.

Temporary discontinuation of Kerendia during trimethoprim, or trimethoprim/sulfamethoxazole treatment may be necessary.

Antihypertensive medicinal products

The risk for hypotension increases with concomitant use of multiple other antihypertensive medicinal products. In these patients, blood pressure monitoring is recommended.

Effect of 40 mg finerenone on CYP3A4 and CYP2C8 substrates

At 40 mg once daily, finerenone is a weak inhibitor of the CYP3A4 enzyme *in vivo*. Co-administration of multiple doses of 40 mg finerenone with the CYP3A4 probe substrate midazolam resulted in a 1.31-fold increase in mean midazolam AUC with no effect on C_{max} . The potentially increased exposure of sensitive CYP3A4 substrates with a narrow therapeutic window needs to be considered when used concomitantly with finerenone 40 mg once daily. A multiple-dose regimen of 20 mg finerenone given once daily for 10 days had no relevant effect on the AUC of the CYP3A4 probe substrate midazolam. Therefore, a clinically relevant inhibition or induction of CYP3A4 by finerenone can be excluded at this dose level.

At 40 mg once daily, finerenone is a weak inhibitor of the CYP2C8 enzyme *in vivo*. Co-administration of multiple doses of 40 mg finerenone with the CYP2C8 probe substrate repaglinide resulted in a 1.59-fold increase in mean repaglinide AUC and a 1.30-fold increase in C_{max} . The potentially increased exposure of CYP2C8 substrates with a narrow therapeutic window needs to be considered when used concomitantly with finerenone 40 mg once daily. A single dose of 20 mg finerenone had no clinically relevant effect on AUC and C_{max} of the CYP2C8 probe substrate repaglinide. Thus, finerenone does not inhibit CYP2C8 at this dose level.

4.6 Fertility, pregnancy and lactation

Contraception in females

Women of childbearing potential should use effective contraception during finerenone treatment (see section 4.4).

Pregnancy

There are no data from the use of finerenone in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Kerendia should not be used during pregnancy unless the clinical condition of the woman requires treatment with finerenone. If the woman becomes pregnant while taking finerenone, she should be informed of potential risks to the foetus (see section 4.4).

Breast-feeding

It is unknown whether finerenone/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of finerenone and its metabolites in milk. Rat pups exposed via this route showed adverse reactions (see section 5.3).

A risk to the newborns/infants cannot be excluded.

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 (see section 4.4).

Fertility

There are no data on the effect of finerenone on human fertility. Animal studies have shown impaired female fertility at exposures considered in excess to the maximum human exposure, indicating low clinical relevance (see section 5.3).

4.7 Effects on ability to drive and use machines

Kerendia has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction under treatment with finerenone was hyperkalaemia (12.6%). See 'Description of selected adverse reactions, *Hyperkalaemia*' below and section 4.4.

Tabulated list of adverse reactions

The safety of finerenone in patients with chronic kidney disease (CKD) and T2D was evaluated in 2 pivotal phase III studies, FIDELIO-DKD (diabetic kidney disease) and FIGARO-DKD. In the FIDELIO-DKD study 2,818 patients received finerenone (10 mg or 20 mg once daily) with a mean duration of treatment of 2.2 years. In the FIGARO-DKD study, 3,671 patients received finerenone (10 mg or 20 mg once daily) with a mean duration of treatment of 2.9 years.

The safety of finerenone in patients with heart failure (HF) with LVEF \geq 40% was evaluated in the phase III study, FINEARTS-HF. In this study, 2,993 patients received finerenone (10 mg, 20 mg, or 40 mg once daily) with a mean duration of treatment of 2.1 years.

The adverse reactions observed are listed in table 3. They are classified according to MedDRA system organ class and frequency convention.

Adverse reactions are grouped according to their frequencies in the order of decreasing seriousness.

Frequencies are defined as follows:

Very common (\geq 1/10), common (\geq 1/100 to $<$ 1/10), uncommon (\geq 1/1,000 to $<$ 1/100), rare (\geq 1/10,000 to $<$ 1/1,000), very rare ($<$ 1/10,000), not known (cannot be estimated from the available data).

Table 3: Adverse reactions

System organ class	Frequency	CKD with T2D	HF with LVEF \geq 40%
Metabolism and nutrition disorders	Very common	Hyperkalaemia	-
	Common	Hyponatraemia Hyperuricaemia	Hyperkalaemia Hyponatraemia Hyperuricaemia
Vascular disorders	Common	Hypotension	Hypotension
Gastrointestinal disorders	Common	-	Diarrhoea Constipation
Skin and subcutaneous tissue disorders	Common	Pruritus	-
Renal and urinary disorders	Common	-	Renal impairment Acute kidney injury
Investigations	Common	Blood creatinine increased/ Glomerular filtration rate decreased	Blood creatinine increased/ Glomerular filtration rate decreased
	Uncommon	Haemoglobin decreased	-

Description of selected adverse reactions*Hyperkalaemia*

An increase from baseline in mean serum potassium in the first month of treatment of up to 0.2 mmol/L was observed in the finerenone group compared to placebo, which remained stable thereafter.

In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, hyperkalaemia events were reported in 14.0% of finerenone-treated patients compared with 6.9% of placebo-treated patients. Serious events of hyperkalaemia were reported more frequently for finerenone (1.1%) than for placebo (0.2%). Serum potassium concentrations > 5.5 mmol/L and > 6.0 mmol/L were reported in 16.8% and 3.3% of finerenone-treated patients and in 7.4% and 1.3% of placebo-treated patients, respectively.

Hyperkalaemia leading to permanent discontinuation in patients who received finerenone was 1.7% versus 0.6% in the placebo group. Hospitalisation due to hyperkalaemia in the finerenone group was 0.9% versus 0.2% in the placebo group.

In the FINEARTS-HF study, hyperkalaemia events were reported in 9.7% of finerenone-treated patients compared with 4.2% of placebo-treated patients. Hyperkalaemia leading to permanent discontinuation in patients who received finerenone was 0.4% versus 0.2% in the placebo group. Hospitalisation due to hyperkalaemia in the finerenone group was 0.5% versus 0.2% in the placebo group.

In all studies, the majority of hyperkalaemia events were mild to moderate and resolved in patients treated with finerenone.

For specific recommendations, see sections 4.2 and 4.4.

Worsening of renal function

In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, GFR decreased events were reported in 5.4% of finerenone-treated patients compared with 4.2% of placebo-treated patients. GFR decreased events leading to permanent discontinuation were the same in patients receiving finerenone or placebo (0.2%). Hospitalisation due to decreased GFR was the same in patients receiving finerenone or placebo (< 0.1%).

Blood creatinine increased events were reported in 2.6% of finerenone-treated patients compared with 2.3% of placebo-treated patients.

The majority of GFR decreased/blood creatinine increased events were mild or moderate and resolved in patients treated with finerenone. Patients on finerenone experienced an initial decrease in eGFR (mean 2 mL/min/1.73 m²) that attenuated over time compared to placebo. This decrease appeared to be reversible during continuous treatment.

In the FINEARTS-HF study, events related to worsening of renal function were reported more frequently in patients treated with finerenone (17.7%) compared to those receiving placebo (10.9%). The reported events included renal impairment (6.6% vs. 3.9%), GFR decreased (5.2% vs. 3.6%), acute kidney injury (3.7% vs. 2.1%), renal failure (2.6% vs. 1.6%), and blood creatinine increased (1.2% vs. 0.8%).

Overall, most of the reported events related to worsening of renal function were mild to moderate and resolved in patients treated with finerenone. In some cases where finerenone was permanently discontinued, eGFR did not return to baseline levels. Events related to worsening of renal function that led to permanent discontinuation were identical in both the finerenone and placebo groups (0.3%). Events related to worsening of renal function leading to hospitalisation were reported more frequently in patients treated with finerenone compared to the placebo group (2.0% vs. 1.3%), with acute kidney injury being the most frequently reported event leading to hospitalisation (1.6% in finerenone vs. 0.8% in placebo).

Patients on finerenone experienced an initial decrease in GFR that appeared to be reversible during continuous treatment. The mean difference in GFR between finerenone and placebo was approximately 3-4 mL/min/1.73 m² from month 1 to month 6. After month 6, the decline in GFR was slightly larger in the placebo group, with a mean difference between finerenone and placebo of approximately 2-3 mL/min/1.73 m².

Hypotension

Finerenone treatment led to a mean systolic blood pressure decrease by 2-4 mm Hg and a mean diastolic blood pressure decrease by 1-2 mm Hg at month 1, remaining stable thereafter.

In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, hypotension events were reported in 4.7% of finerenone-treated patients compared with 3.0% of placebo-treated patients. In 3 patients (< 0.1%), finerenone treatment was permanently discontinued due to hypotension. Hospitalisation due to hypotension was the same in patients receiving finerenone or placebo (0.1%).

In the FINEARTS-HF study, hypotension events were reported in 7.6% of finerenone-treated patients compared with 4.7% of placebo-treated patients. In 3 patients (0.1%), finerenone treatment was permanently discontinued due to hypotension. Hospitalisation due to hypotension was 0.4% in the finerenone group versus 0.3% in the placebo group.

In all studies, the majority of hypotension events were mild or moderate and resolved in patients treated with finerenone.

Hyperuricaemia

In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, hyperuricaemia events were reported in 5.1% of finerenone-treated patients compared with 3.9% of placebo-treated patients. An increase from baseline in mean serum uric acid of 0.3 mg/dL was seen in the finerenone group compared to placebo up to month 16, which attenuated over time. Gout reporting was comparable in finerenone-treated patients (3.1%) and in placebo-treated patients (3.0%).

In the FINEARTS-HF study, hyperuricaemia reporting was comparable in finerenone-treated patients (2.7%) and in placebo-treated patients (2.4%). Gout reporting was comparable in finerenone-treated patients (2.4%) and in placebo-treated patients (2.8%).

In all studies, hyperuricaemia events were non-serious and did not result in permanent discontinuation in patients who received finerenone.

Gastrointestinal disorders

In the FINEARTS-HF study, diarrhoea (5.7% vs. 4.4%) and constipation (3.8% vs. 2.7%) were reported more frequently for finerenone compared with placebo.

Haemoglobin decreased

In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, finerenone was associated with a placebo-corrected absolute decrease in mean haemoglobin of 0.15 g/dL and mean haematocrit of 0.5% after 4 months of treatment. Anaemia reporting was comparable in finerenone-treated patients (6.5%) and placebo-treated patients (6.1%). The frequency of serious events of anaemia was low in both the finerenone-treated and placebo-treated patients (0.5%). Changes in haemoglobin and haematocrit were transient and reached comparable levels to those observed in the placebo-treated group after about 24-32 months.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Pharmacotherapeutic group: diuretics, aldosterone antagonists, ATC code: C03DA05

Mechanism of action

Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR) which is activated by aldosterone and cortisol and regulates gene transcription. 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.

Pharmacodynamic effects

In FIDELIO-DKD and FIGARO-DKD, randomised, double-blind, placebo-controlled, multicentre phase III studies in adult patients with CKD and T2D, the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio (UACR) in patients randomised to finerenone was 31% and 32%, respectively at month 4 and UACR remained reduced throughout both studies.

In FINEARTS-HF, randomised, double-blind, placebo-controlled, multicentre phase III study in adult patients with HF with LVEF \geq 40%, the placebo-corrected relative reduction in UACR in patients randomised to finerenone was 30% at month 6, and UACR remained reduced up to the last measurement at year 2.

In ARTS-DN, a randomised, double-blind, placebo-controlled, multicentre phase IIb study in adult patients 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

A dedicated QT study in 57 healthy participants showed that finerenone has no effect on cardiac repolarisation. There was no indication of a QT/QTc prolonging effect of finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic).

Clinical efficacy and safety

Chronic kidney disease associated with T2D

The FIDELIO-DKD and FIGARO-DKD studies investigated the effect of finerenone compared to placebo on kidney and cardiovascular (CV) outcomes in adult patients with CKD and T2D.

Patients 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).

Patients with diagnosed heart failure with reduced ejection fraction and NYHA class II-IV were excluded due to the class 1A recommendation for MRA therapy.

In the FIDELIO-DKD study 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/1.73 m² and serum potassium ≤ 4.8 mmol/L at screening.

The primary endpoint 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/1.73 m² 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 CV death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalisation for heart failure.

A total of 5,662 patients were randomised to receive either finerenone (N = 2,824) or placebo (N = 2,838) and included in the analyses. The median follow-up was 2.6 years. The dose of finerenone or placebo could be adjusted between 10 mg and 20 mg once daily during the course of the study, based mainly on serum potassium concentration. At month 24, of the subjects treated with finerenone, 67% were treated with 20 mg once daily, 31% with 10 mg once daily and 3% were on a treatment interruption.

After the end of study, vital status was obtained for 99.7% of patients. The study 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 44.4 mL/min/1.73 m², with 55% of patients having an eGFR < 45 mL/min/1.73 m², median UACR was 853 mg/g, and mean HbA1c was 7.7%, 46% had a history of atherosclerotic CV disease, 30% a history of coronary artery disease, 8% a history of cardiac failure, and the mean blood pressure was 138/76 mm Hg. The mean duration of T2D at baseline was 16.6 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 47% and 26% of patients, respectively. At baseline, almost all patients were on ACEi (34%) or ARB (66%), and 97% of patients used one or more antidiabetic medicinal products (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). The other most frequent medicinal products taken at baseline were statins (74%) and calcium channel blockers (63%).

A statistically significant difference in favour of finerenone was shown for the primary composite endpoint and the key secondary composite endpoint (see figure 1/table 4 below). The treatment effect for the primary and key secondary endpoints was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure (SBP) and HbA1c at baseline.

In the FIGARO-DKD study patients were eligible, based on evidence of persistent albuminuria having an UACR of ≥ 30 mg/g to < 300 mg/g and an eGFR of 25 to 90 mL/min/1.73 m², or an UACR ≥ 300 mg/g and an eGFR ≥ 60 mL/min/1.73 m² at screening. Patients were required to have a serum potassium of ≤ 4.8 mmol/L at screening.

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

A total of 7,328 patients were randomised to receive either finerenone (N = 3,674), or placebo (N = 3,654) and included in the analyses. The median follow-up was 3.4 years. The dose of finerenone or placebo could be adjusted between 10 mg and 20 mg once daily during the course of the study, based mainly on serum potassium concentration. At month 24, of the subjects treated with finerenone, 82% were treated with 20 mg once daily, 15% with 10 mg once daily and 3% were on a treatment interruption. After the end of study, vital status was obtained for 99.8% of patients. The study population was 72% White, 20% Asian and 4% Black. The mean age at enrolment was 64 years and 69% of patients were male. At baseline, the mean eGFR was 67.8 mL/min/1.73 m², with 62% of patients having an eGFR \geq 60 mL/min/1.73 m², median UACR was 309 mg/g, and mean HbA1c was 7.7%, 45% of patients had a history of atherosclerotic CV disease, 8% had a history of cardiac failure, and the mean blood pressure was 136/77 mm Hg. The mean duration of T2D 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, almost all patients were on ACEi (43%) or ARB (57%), and 98% of patients used one or more antidiabetic medicinal products (insulin [54%], biguanides [69%], GLP-1 receptor agonists [8%], SGLT2 inhibitors [8%]). The other most frequent medicinal products taken at baseline were statins (71%).

A statistically significant difference in favour of finerenone was shown for the CV primary composite endpoint (see figure 2/table 5 below). The treatment effect for the primary endpoint was consistent across subgroups, including region, eGFR, UACR, SBP and HbA1c at baseline.

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 finerenone group compared to placebo, however this difference did not achieve statistical significance (see table 5 below). The treatment effect for the kidney secondary composite endpoint was consistent across subgroups of eGFR at baseline, but for the subgroup of patients with UACR < 300 mg/g the HR was 1.16 (95% CI 0.91; 1.47) and for the subgroup of patients with UACR \geq 300 mg/g the HR was 0.74 (95% CI 0.61; 0.89).

Additional prespecified secondary time-to-event endpoints are included in table 5.

Table 4: Analysis of the primary and secondary time-to-event endpoints (and their individual components) in phase III study FIDELIO-DKD

	Kerendia* (N = 2,824)		Placebo (N = 2,838)		Treatment effect
	N (%)	Events/ 100-pyr	N (%)	Events/ 100-pyr	HR (95% CI)
Primary renal composite endpoint and its components					
Composite of kidney failure, sustained eGFR decline \geq 40% or renal death	498 (17.6)	7.53	600 (21.1)	9.09	0.82 (0.73; 0.92) p = 0.0009
Kidney failure	205 (7.3)	2.96	235 (8.3)	3.39	0.86 (0.72; 1.05)
Sustained eGFR decline \geq 40%	473 (16.7)	7.15	577 (20.3)	8.74	0.81 (0.72; 0.91)
Renal death	2 (< 0.1)	-	2 (< 0.1)	-	-
Key secondary CV composite endpoint and its components					
Composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for heart failure	366 (13.0)	5.11	420 (14.8)	5.93	0.86 (0.75; 0.99) p = 0.0344
CV death	128 (4.5)	1.70	150 (5.3)	1.99	0.86 (0.68;1.09)
Non-fatal MI	70 (2.5)	0.94	87 (3.1)	1.18	0.80 (0.58;1.09)
Non-fatal stroke	90 (3.2)	1.22	87 (3.1)	1.18	1.03 (0.77;1.38)
Hospitalisation for heart failure	138 (4.9)	1.88	162 (5.7)	2.22	0.85 (0.68;1.07)
Secondary efficacy endpoints					
All-cause mortality	219 (7.8)	2.90	244 (8.6)	3.24	0.90 (0.75; 1.08) **
All-cause hospitalisation	1,259 (44.6)	22.59	1,321 (46.5)	23.91	0.95 (0.88; 1.02) **
Composite of kidney failure, sustained eGFR decline \geq 57% or renal death	248 (8.8)	3.60	326 (11.5)	4.74	0.75 (0.65; 0.90) **

* Treatment with 10 or 20 mg once daily in addition to maximum tolerated labelled doses of ACEi or ARB.

** p= not statistically significant after adjustment for multiplicity

CI: Confidence interval

HR: Hazard ratio

pyr: patient-years

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

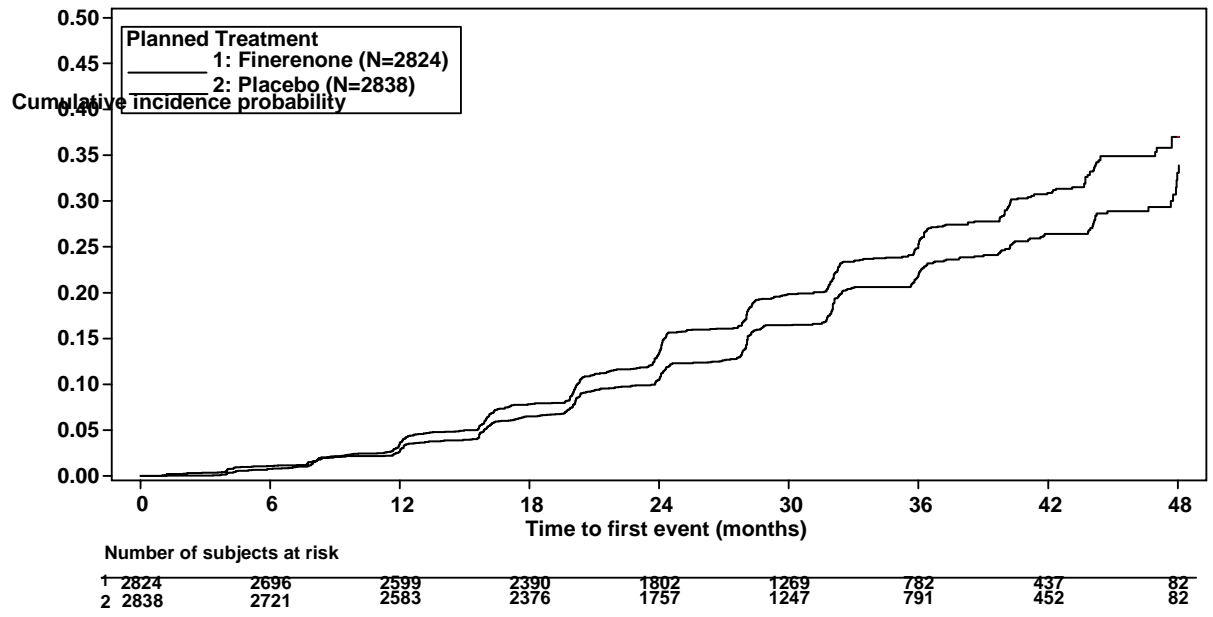


Table 5: Analysis of the primary and secondary time-to-event endpoints (and their individual components) in phase III study FIGARO-DKD

	Kerendia* (N = 3,674)		Placebo (N = 3,654)		Treatment effect
	N (%)	Events/ 100-pyr	N (%)	Events/ 100-pyr	HR (95% CI)
Primary CV composite endpoint and its components					
Composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for heart failure	457 (12.4)	3.88	518 (14.2)	4.46	0.87 (0.76; 0.98) p = 0.0254
CV death	193 (5.3)	1.56	214 (5.9)	1.75	0.89 (0.73; 1.08)
Non-fatal MI	103 (2.8)	0.85	101 (2.8)	0.84	1.00 (0.76; 1.32)
Non-fatal stroke	108 (2.9)	0.89	111 (3.0)	0.93	0.97 (0.74; 1.26)
Hospitalisation for heart failure	117 (3.2)	0.97	163 (4.5)	1.36	0.71 (0.56; 0.90)
Secondary renal composite endpoint and its components					
Composite of kidney failure, sustained eGFR decline \geq 40% or renal death	350 (9.5)	3.17	395 (10.8)	3.59	0.87 (0.75; 1.01) p = 0.0635 **
Kidney failure	46 (1.3)	0.40	62 (1.7)	0.55	0.72 (0.49; 1.05)
Sustained eGFR decline \geq 40%	338 (9.2)	3.06	385 (10.5)	3.50	0.86 (0.74; < 1.00)
Renal death	0	-	2 (< 0.1)	-	-
Secondary efficacy endpoints					
All-cause mortality	332 (9.0)	2.69	370 (10.1)	3.03	0.89 (0.77; 1.03) **
All-cause hospitalisation	1,569 (42.7)	16.94	1,599 (43.8)	17.54	0.97 (0.90; 1.04) **
Composite of kidney failure, sustained eGFR decline \geq 57% or renal death	108 (2.9)	0.95	139 (3.8)	1.23	0.77 (0.60; 0.99) **

* Treatment with 10 or 20 mg once daily in addition to maximum tolerated labelled doses of ACEi or ARB.

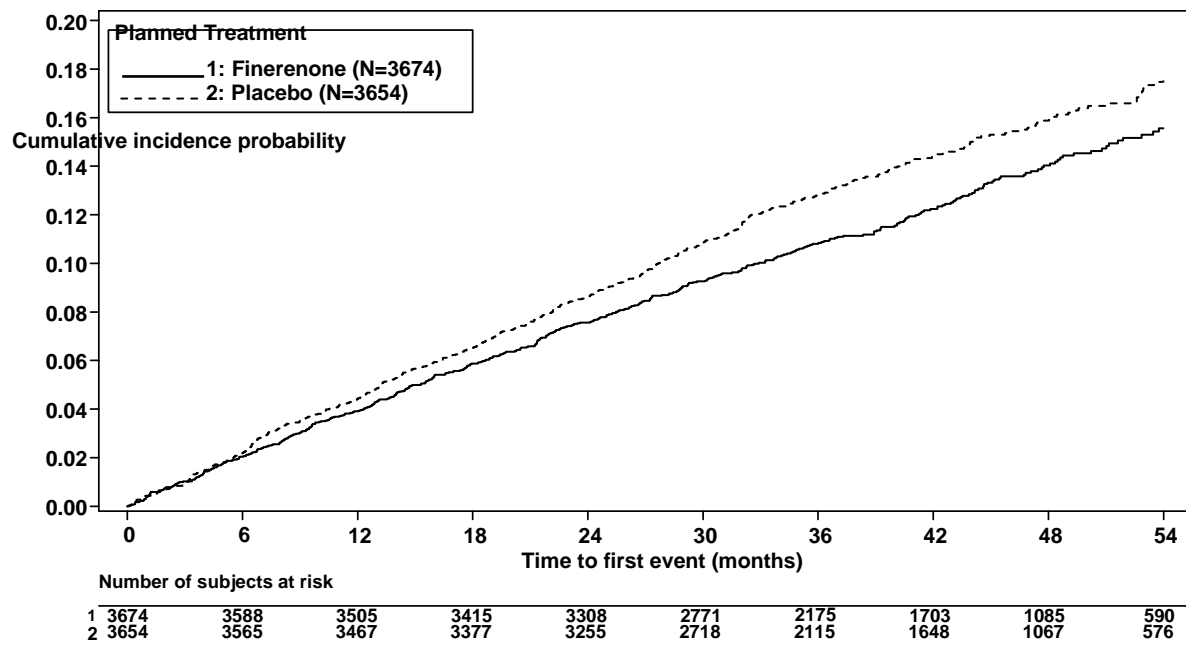
** p=not statistically significant after adjustment for multiplicity

CI: Confidence interval

HR: Hazard ratio

pyr: patient-years

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



Heart failure with LVEF $\geq 40\%$

The FINEARTS-HF study investigated the effect of finerenone compared to placebo on cardiovascular outcomes in adult patients with heart failure.

Patients were eligible with a diagnosis of heart failure with NYHA class II-IV, ambulatory or hospitalised primarily for heart failure, and with documented LVEF $\geq 40\%$. In addition, patients had an eGFR ≥ 25 mL/min/1.73 m² and serum potassium ≤ 5.0 mmol/L at screening and randomisation and were receiving background therapy, including diuretic treatment.

The primary endpoint was the composite of cardiovascular death and total (first and recurrent) heart failure events comprised of hospitalisation for heart failure and urgent heart failure visits. A multiple-testing procedure was used for the secondary endpoints, including total (first and recurrent) heart failure events, and change from baseline to month 6, 9, and 12 in Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) (which quantifies heart failure symptom frequency and severity).

The study analysed 6,001 patients randomly assigned to receive either finerenone (N=3,003) or placebo (N=2,998). The median follow-up was 2.7 years. The study included 3,247 (54%) patients with a heart failure event in the past 3 months, including 1 219 (20%) patients randomised during the hospitalisation or within 7 days of discharge.

Based on renal parameters, patients received either 10 mg, 20 mg or 40 mg finerenone or placebo once daily during the course of the study. At month 24, of the subjects treated with finerenone, 35% were treated with 40 mg once daily, 32% with 20 mg once daily, 12% with 10 mg once daily and 1% were on a treatment interruption. At any time during treatment approximately 80% of the patients reached their target dose. After the end of study notification, vital status was obtained for 99.7% of patients. The study population was 79% White, 17% Asian and 1.5% Black. The mean age at enrolment was 72 years and 46% of patients were female. At baseline, the mean LVEF was 53%, with 64% of patients having an LVEF $\geq 50\%$, and 69%, 30% and 1% of patients were NYHA class II, III and IV, respectively. Mean blood pressure was

129/75 mm Hg while BMI was 30 kg/m². The median N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) was 1,041 pg/mL, the mean eGFR was 62 mL/min/1.73 m² with 48% of patients having an eGFR \leq 60 mL/min/1.73 m², and the median UACR was 18 mg/g. Atrial fibrillation was present for 38% of patients and 41% had diabetes mellitus. The majority of patients were on loop diuretics (87%), an ACEi or ARB (79%), or an angiotensin receptor neprilysin inhibitor (9%), and 14% were on SGLT2 inhibitors.

A statistically significant difference in favour of finerenone was shown for the primary composite endpoint (see table 6 below). The effect was observed early and was sustained throughout the duration of the study (see figure 3 below). A statistically significant difference in favour of finerenone was also shown for the secondary endpoints of total heart failure events. Prespecified secondary efficacy endpoints are also included in table 6 below. The treatment effect for the primary and key secondary endpoints was consistent across all prespecified subgroups, including gender, LVEF, NYHA class, eGFR, time since latest heart failure event, SGLT2 inhibitor therapy, and diabetes mellitus status.

Table 6: Analysis of the primary and secondary endpoints (and their individual components for time-to-event endpoints) in phase III study FINEARTS-HF

	Kerendia* (N = 3,003)		Placebo (N = 2,998)		Treatment effect
	[Event total] N (%)	Events/ 100-pyr	[Event total] N (%)	Events/ 100-pyr	(95% CI)
Primary CV composite endpoint and its components					
Composite of CV death and total heart failure events	[1 083] 624 (20.8)	14.88	[1 283] 719 (24.0)	17.70	RR 0.84 (0.74; 0.95) p = 0.0072
Total heart failure event**	[842] 479 (16.0)	11.57	[1 024] 573 (19.1)	14.12	RR 0.82 (0.71; 0.94) p = 0.0062
CV death	242 (8.1)	3.33	260 (8.7)	3.59	HR 0.93 (0.78; 1.11)
Secondary efficacy endpoints					
Change from baseline in KCCQ-TSS	LSM 7.99	-	LSM 6.43	-	LSM difference 1.56 (0.79; 2.34) p < 0.0001
Improvement in NYHA class	557 (18.6) N = 3 002	-	553 (18.4)	-	OR 1.01 (0.88; 1.15) p = 0.9295 [†]
Renal composite endpoint	75 (2.5)	1.16	55 (1.8)	0.85	HR 1.33 (0.94; 1.89) p ^{††}
Sustained eGFR decrease ≥ 50%	68 (2.3)	1.05	51 (1.7)	0.79	-
Sustained eGFR decline to < 15mL/min/1.73m ²	5 (0.2)	0.08	2 (< 0.1)	0.03	-
Initiation of dialysis	2 (< 0.1)	0.03	2 (< 0.1)	0.03	-
Renal transplantation	0 (0.0)	0.00	0 (0.0)	-	-
All-cause mortality	491 (16.4)	6.71	522 (17.4)	7.17	HR 0.93 (0.83; 1.06)

Abbreviations: CI: Confidence interval; HR: Hazard ratio; LSM: Least squares mean; OR: Odds ratio; RR: Rate ratio; pyr: patient-years

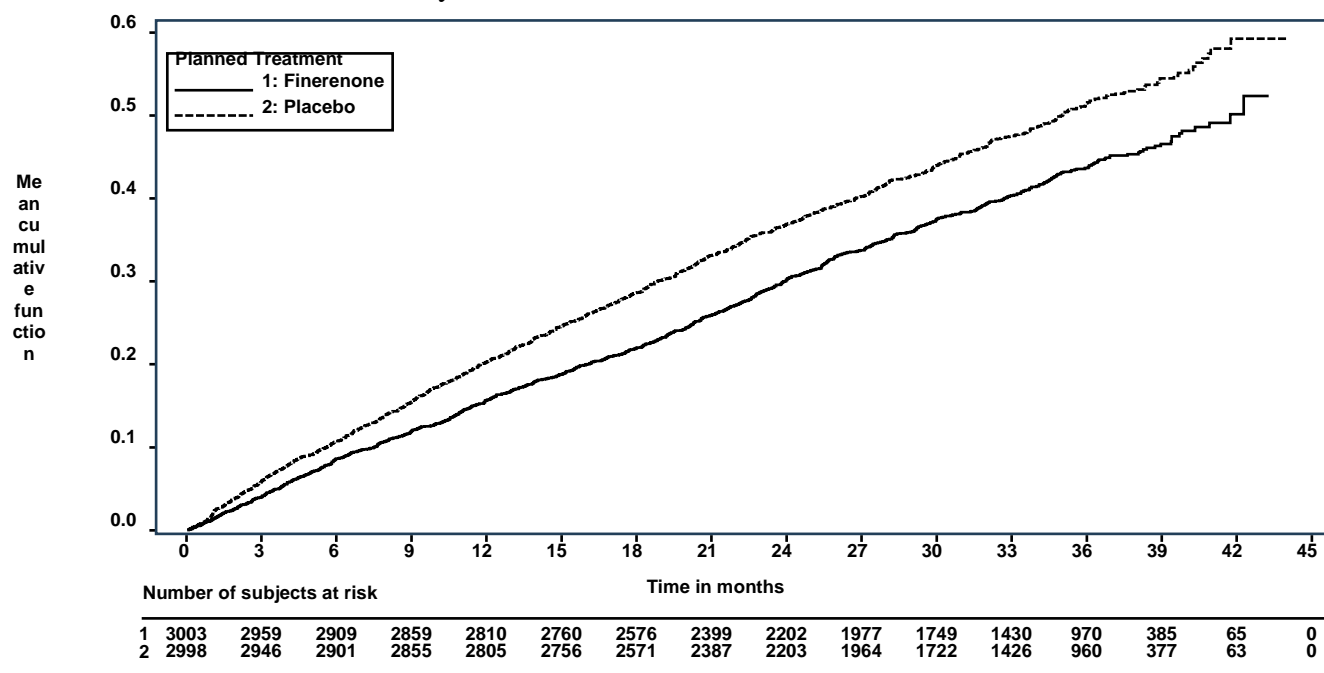
* Treatment with 10, 20 or 40 mg once daily in addition to background therapy, including diuretic treatment

** Total (first and recurrent) heart failure events was also a key secondary endpoint

† Not significant (testing procedure stopped)

†† Endpoint not formally tested (preceding endpoint in testing procedure not significant)

Figure 3: Primary composite endpoint of CV death and total (first and recurrent) heart failure events in the FINEARTS-HF study



Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with Kerendia in one or more subsets of the paediatric population in treatment of chronic kidney disease and heart failure (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 a substrate of the efflux transporter P-glycoprotein *in vitro*, which is however not considered relevant for its absorption *in vivo* due to the high permeability of finerenone.

Effect of food

Intake with high fat, high calorie food increased finerenone AUC by up to 21%, reduced C_{max} by 19% to 23% and prolonged the time to reach C_{max} up to 2.5 hours. Since this is not considered as clinically relevant, finerenone can be taken with or without food.

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.

Biotransformation

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. Four major metabolites were found in plasma. 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. Systemic blood clearance of finerenone is about 25 L/h. About 80% of the administered dose was excreted via urine and approximately 20% of the dose was excreted via faeces. Excretion was almost exclusively in the form of metabolites, while excretion of unchanged finerenone represents a minor route (< 1% of dose in the urine due to glomerular filtration, < 0.2% in the faeces).

Linearity

Finerenone pharmacokinetics are linear across the investigated dose range from 1.25 to 80 mg given as single dose tablets.

Special populations

Elderly

Of the 2,818 patients who received finerenone in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. Of the 3,671 patients who received finerenone in the FIGARO-DKD study, 53% of patients were 65 years and older, and 14% were 75 years and older. Of the 2,993 patients who received finerenone in the FINEARTS-HF study, 79% of patients were 65 years and older, and 43% were 75 years and older.

In a phase I study (N = 48) elderly healthy participants (≥ 65 years of age) exhibited higher finerenone plasma concentrations than younger healthy participants (≤ 45 years of age), with mean AUC and C_{max} values being 34% and 51% higher in the elderly (see section 4.2). Population-pharmacokinetic analyses did not identify age as a covariate for finerenone AUC or C_{max} .

Renal impairment

Mild renal impairment (creatinine clearance [CL_{CR}] 60 to < 90 mL/min) did not affect finerenone AUC and C_{max} .

Compared to patients with normal renal function ($CL_{CR} \geq 90$ 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 effect on C_{max} (see section 4.2).

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

Hepatic impairment

There was no change in finerenone exposure in cirrhotic patients with mild hepatic impairment (see section 4.2).

In cirrhotic patients with moderate hepatic impairment, finerenone total and unbound AUC were increased by 38% and 55%, respectively, while no change in C_{\max} was observed compared to healthy control participants (see section 4.2).

There are no data in patients with severe hepatic impairment (see sections 4.2 and 4.5).

Body weight

Population-pharmacokinetic analyses identified body weight as a covariate for finerenone C_{\max} and AUC. C_{\max} and AUC of subjects with a body weight of below 57 kg were estimated to be, on average, 52% and 30% higher, respectively, and of subjects with a body weight above 122 kg, 32% and 20% lower, respectively, compared to subjects between 57 and 122 kg. Dose adaptation based on body weight is not warranted (see section 4.2).

Pharmacokinetic/pharmacodynamic relationships

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 an indirect and delayed effect on pharmacodynamic responses.

Clinical studies with no relevant drug-drug interactions

Concomitant use of gemfibrozil (600 mg twice daily), a strong inhibitor of CYP2C8, increased finerenone mean AUC and C_{\max} 1.1-fold and 1.2-fold, respectively. This is not considered as 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 considered as clinically relevant.

Lack of mutual pharmacokinetic interaction was demonstrated between finerenone and the CYP2C9 substrate warfarin and between finerenone and the P-gp substrate digoxin.

Multiple doses of 40 mg finerenone once daily had no clinically relevant effect on AUC and C_{\max} of the breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP) substrate rosuvastatin.

5.3 Preclinical safety data

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

Repeated dose toxicity

In dogs, a reduced prostate weight and size was found at an $AUC_{unbound}$ of about 4 to 60 times that in humans. The dose free of findings provides a safety margin of about 1-2.

Carcinogenic potential

In 2-year carcinogenicity studies, finerenone did not show carcinogenic potential in male and female rats or female mice. In male mice, finerenone resulted in an increase in Leydig cell adenoma at doses representing 10 to 26 times the $AUC_{unbound}$ in humans. A dose representing 7 times the $AUC_{unbound}$ for the 40 mg dose and 17 times the $AUC_{unbound}$ in humans for the 20 mg did not cause any tumours. Based on the known sensitivity of rodents to develop these tumours and the pharmacology-based mechanism at suprathreshold doses as well as adequate safety margins, the increase in Leydig cell tumours in male mice is not clinically relevant.

Toxicity to development

In the embryo-foetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of foetal toxicity, including reduced foetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of at least 7 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight oedema, shortened umbilical cord, slightly enlarged fontanelle) and one foetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 10 times that in humans at the dose of 40 mg and about 25 times that in humans at the dose of 20 mg. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 4 to 13 times for $AUC_{unbound}$. Therefore, the findings in rats do not indicate an increased concern for foetal harm.

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 2 or 4 times the $AUC_{unbound}$ expected in humans at the dose of 40 mg and 20 mg, respectively. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioural changes starting at about 2 or 4 times the $AUC_{unbound}$ expected in humans at the dose of 40 mg and 20 mg, respectively. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$ for the 20 mg dose and is in the therapeutic range for the 40 mg dose. The increased locomotor activity in offspring may indicate a potential risk for the foetus. In addition, because of the findings in pups, a risk for the nursing newborn/infant cannot be excluded.

Female fertility

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 foetuses) at about 9 times the human AUC_{unbound} for the 40 mg dose and at about 21 times the human AUC_{unbound} for the 20 mg dose. In addition, reduced ovarian weights were found at about 7 times the human AUC_{unbound} for the 40 mg dose and at about 17 times the human AUC_{unbound} for the 20 mg dose. No effects on female fertility and early embryonic development were found at 4 times the human AUC_{unbound} for the 40 mg dose and 10 times the human AUC_{unbound} for the 20 mg dose. Therefore, the findings in female rats are of little clinical relevance (see section 4.6).

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that finerenone may pose a risk for the surface water and groundwater compartment (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline (E 460)
Croscarmellose sodium
Hypromellose 2910 (E 464)
Lactose monohydrate
Magnesium stearate (E 470b)
Sodium laurilsulfate (E 487)

Tablet coating

Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Talc (E 553b)
Iron oxide red (E 172)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium transparent calendarised blisters with 14 film-coated tablets.
Pack sizes of 14, 28 or 98 film-coated tablets.

PVC/PVDC/Aluminium transparent perforated unit dose blisters with
10 x 1 film-coated tablets. Pack size of 100 × 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance
with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0766

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2026

10 DATE OF REVISION OF THE TEXT

10/04/2026

