PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

FIRIALTA® 10 mg film-coated tablets
FIRIALTA® 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FIRIALTA 10 mg film-coated tablets

Each film-coated tablet contains 10 mg finerenone.

Excipient with known effect

Each film-coated tablet contains 45 mg lactose (as monohydrate), see section 4.4.

FIRIALTA 20 mg film-coated tablets

Each film-coated tablet contains 20 mg finerenone.

Excipient with known effect

Each film-coated tablet contains 40 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

FIRIALTA 10 mg film-coated tablets
Pink, oval-oblong film-coated tablet with a length of 10 mm and a width of 5 mm, marked ‘10’ on one side and ‘FI’ on the other side.

FIRIALTA 20 mg film-coated tablets
Yellow, oval-oblong film-coated 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

FIRIALTA is indicated for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults.

For study results with respect to renal and cardiovascular events, see section 5.1.

4.2 Posology and method of administration

Posology

The recommended target dose is 20 mg finerenone once daily.
The maximum recommended dose is 20 mg finerenone once daily.

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

If serum potassium ≤ 4.8 mmol/L, finerenone treatment can be initiated. For monitoring of serum potassium, see below 'Continuation of treatment'.

If serum potassium > 4.8 to 5.0 mmol/L, initiation of finerenone 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).

If serum potassium > 5.0 mmol/L, finerenone treatment should not be initiated (see section 4.4).

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 m^2)	**Starting dose (once daily)**
≥ 60	20 mg
≥ 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 increase in dose (see table 2 to determine continuation of finerenone treatment and dose adjustment).
Thereafter, serum potassium has to be remeasured periodically and as needed based on patient characteristics and serum potassium levels.
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**
Current serum potassium (mmol/L)	≤ 4.8	Increase to 20 mg finerenone once daily*	Maintain 20 mg once daily
	> 4.8 to 5.5	Maintain 10 mg once daily	Maintain 20 mg once daily
	> 5.5	Withhold finerenone. Consider re-starting at 10 mg once daily when serum potassium ≤ 5.0 mmol/L.	Withhold finerenone. Re-start at 10 mg once daily when serum potassium ≤ 5.0 mmol/L.

* maintain 10 mg once daily, if eGFR has decreased > 30% compared to the previous measurement

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
No dose adjustment is necessary in elderly patients (see section 5.2).

Renal impairment
Initiation of treatment
In patients with eGFR < 25 mL/min/1.73 m^2, finerenone treatment should not be initiated due to limited clinical data (see sections 4.4 and 5.2).

Continuation of treatment
In patients with eGFR ≥ 15 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 to the recommended daily dose of 20 mg (see 'Posology, Continuation of treatment' and table 2).
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 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 medication
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 ('Posology, 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, FIRIALTA 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.

Initiation and continuation of treatment (see section 4.2)
If serum potassium > 5.0 mmol/L, finerenone treatment should not be initiated.
If serum potassium > 4.8 to 5.0 mmol/L, initiation of finerenone treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels.

If serum potassium > 5.5 mmol/L, finerenone treatment has to be withheld. Local guidelines for the management of hyperkalaemia have to be followed.
Once serum potassium ≤ 5.0 mmol/L, finerenone treatment can be restarted at 10 mg once daily.

Monitoring
Serum potassium and eGFR have to be remeasured in all patients 4 weeks after initiation, re-start or increase in dose 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).

Concomitant medications
The risk of hyperkalaemia also may increase with the intake of concomitant medications that may increase serum potassium (see section 4.5.). See also ‘Concomitant use of substances that affect finerenone exposure’ in this section.

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.
- trimethoprim, or trimethoprim/sulfamethoxazole. Temporary discontinuation of finerenone may be necessary.

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 m^2 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 m^2).

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).

Heart failure

Patients with diagnosed heart failure with reduced ejection fraction and New York Heart Association II-IV were excluded from the phase III clinical studies (see section 5.1).

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. 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

FIRIALTA contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

FIRIALTA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicines 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 FIRIALTA 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
FIRIALTA 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 medicine that increase serum potassium
FIRIALTA 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 medicines 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 medicines that increase serum potassium (see section 4.4)
Concomitant use of FIRIALTA 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 FIRIALTA during trimethoprim, or trimethoprim/ sulfamethoxazole treatment may be necessary.

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

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).

FIRIALTA should not be used during pregnancy. 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.
Women who breastfeed their babies should not take FIRIALTA.

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

FIRIALTA 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 (14.0%). 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 type 2 diabetes (T2D) was evaluated in 2 pivotal phase III studies, FIDELIO-DKD (diabetic kidney disease) and FIGARO-DKD. In the FIDELIO-DKD study 2,827 patients received finerenone (10 or 20 mg once daily) with a mean duration of treatment of 2.2 years. In the FIGARO-DKD study, 3,683 patients received finerenone (10 or 20 mg once daily) with a mean duration of treatment of 2.9 years.

The adverse reactions observed are listed in table 3. They are classified according to MedDRA`s system organ class database and frequency convention.
Adverse reactions are grouped according to their frequencies in the order of decreasing seriousness.
Frequencies are defined, as follows:
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), not known (cannot be estimated from the available data)

Table 3: Adverse reactions

System Organ Class (MedDRA)	**Very common**	**Common**	**Uncommon**
Metabolism and nutrition disorders	Hyperkalaemia	Hyponatraemia Hyperuricaemia	
Vascular disorders		Hypotension	
Skin and subcutaneous tissue disorders		Pruritus	
Investigations		Glomerular filtration rate decreased	Haemoglobin decreased

Description of selected adverse reactions

Hyperkalaemia
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.
An increase from baseline in mean serum potassium in the first month of treatment of 0.17 mmol/L was observed in the finerenone group compared to placebo, which remained stable thereafter.
The majority of hyperkalaemia events were mild to moderate and resolved in patients treated with finerenone.

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 1.2% 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.
For specific recommendations, refer to sections 4.2 and 4.4.

Hypotension
In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, hypotension events were reported in 4.6% 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 %).
The majority of hypotension events were mild or moderate and resolved in patients treated with finerenone.
The mean systolic blood pressure decreased by 2-4 mm Hg and the mean diastolic blood pressure decreased by 1-2 mm Hg at month 1, remaining stable thereafter.

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. All events were non-serious and did not result in permanent discontinuation in patients who received finerenone. 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. No difference between the finerenone group and the placebo group was observed for reported events of gout (3.0%).

Glomerular filtration rate (GFR) decreased
In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, GFR decreased events were reported in 5.3% of finerenone-treated patients compared with 4.2% of placebo-treated patients. In patients treated with finerenone, the majority of GFR decreased events were mild or moderate and resolved. 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%).
The majority of GFR decreased 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 m^2) that attenuated over time compared to placebo. This decrease appeared to be reversible during continuous treatment.

Haemoglobin decreased
In the pooled data of FIDELIO-DKD and FIGARO-DKD studies, finerenone was associated with a change in mean haemoglobin of -0.17 g/dL and mean haematocrit of -0.46% compared with -0.02 g/dL and 0.03% under placebo, respectively 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 medicines is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternatively, you can report to Bayer SafeTrack site (https://www.safetrack-public.bayer.com).

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

Category and class: A 18.10 Medicines acting on reno- urinary and genital system

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 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

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 New York Heart Association II-IV were excluded due to the class 1A recommendation for MRA therapy.

In the FIDELIO-DKD study, patients were selected based on criteria including persistent albuminuria (greater than 30 mg/g), an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73 m^2, and serum potassium levels of 4.8 mmol/L or lower. The primary endpoint of this study was a composite measure that included kidney failure, a sustained decline in eGFR of 40% or more, and renal death. The key secondary endpoint focused on cardiovascular (CV) outcomes, including CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for

heart failure. A total of 5,674 patients were randomized to receive either finerenone (2,833 patients) or a placebo (2,841 patients), with a median follow-up period of 2.6 years. The results indicated statistically significant benefits for finerenone regarding both the primary and key secondary endpoints across various subgroups.

In the FIGARO-DKD study, eligibility criteria included patients with a urinary albumin-to-creatinine ratio (UACR) of 30 mg/g or higher and an eGFR ranging from 25 to 90 mL/min/1.73 m², or a UACR of 300 mg/g or more with an eGFR of at least 60 mL/min/1.73 m², alongside serum potassium levels of 4.8 mmol/L or lower. The primary endpoint in this study was a composite of cardiovascular events, while the secondary endpoint included measures of kidney failure, a sustained decline in eGFR of 40% or more, and renal death. A total of 7,352 patients were randomized, with 3,686 receiving finerenone and 3,666 receiving a placebo, and the median follow-up was 3.4 years. The findings revealed a statistically significant advantage for finerenone concerning the primary CV endpoint, although the secondary outcomes related to kidney failure did not reach statistical significance. The treatment effects were consistent across different patient subgroups in both studies.

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

	FIRIALTA * (N = 2,833)		Placebo (N = 2,841)		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 ≥ 40% or renal death	504 (17.8)	7.59	600 (21.1)	9.08	0.82 (0.73; 0.93) p = 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)	-	-
Key secondary CV composite endpoint and its components					
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) p = 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)
Secondary efficacy endpoints					
All-cause mortality	219 (7.7)	2.90	244 (8.6)	3.23	0.90 (0.75; 1.07) **
All-cause hospitalisation	1,263 (44.6)	22.56	1,321 (46.5)	23.87	0.95 (0.88; 1.02) **
Composite of 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 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 ≥ 40% from baseline, or renal death in the FIDELIO-DKD study

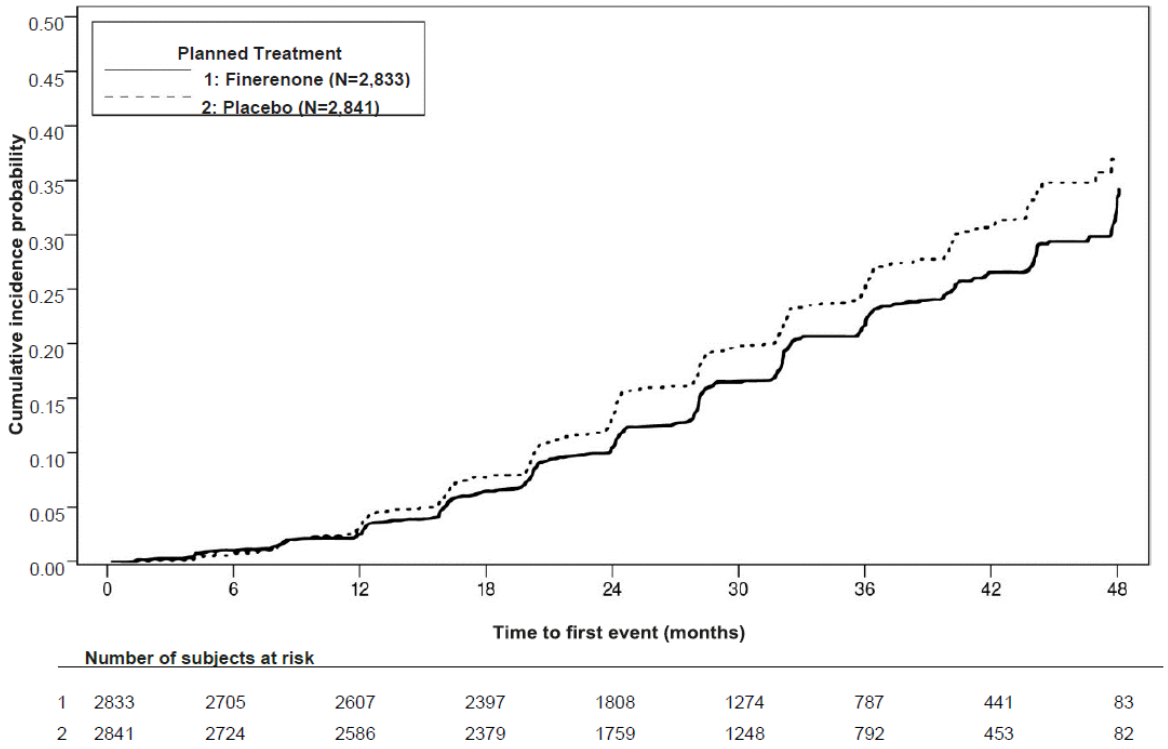
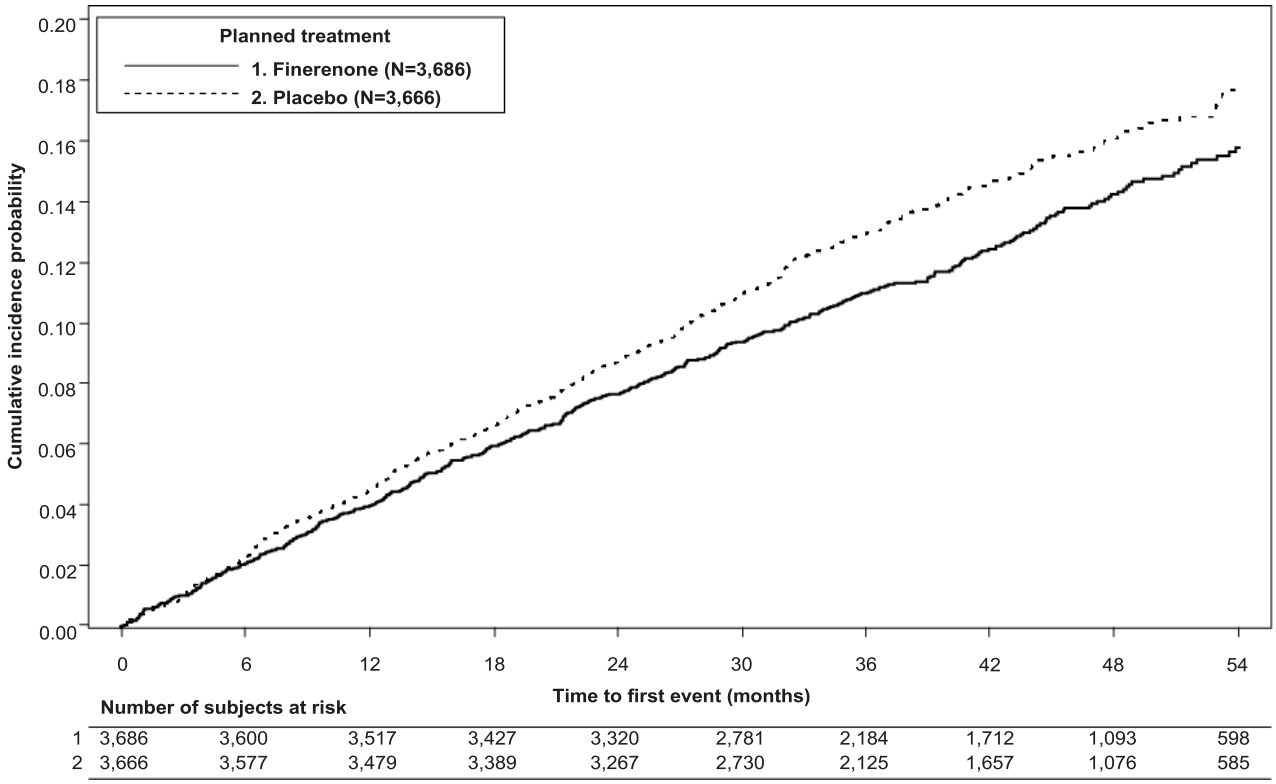


Table 5: Analysis of the primary and secondary time-to-event endpoints (and their individual components) in phase III study FIGARO-DKD

	FIRIALTA* (N = 3,686)		Placebo (N = 3,666)		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	458 (12.4)	3.87	519 (14.2)	4.45	0.87 (0.76; 0.98) p = 0.0264
CV death	194 (5.3)	1.56	214 (5.8)	1.74	0.90 (0.74; 1.09)
Non-fatal MI	103 (2.8)	0.85	102 (2.8)	0.85	0.99 (0.76; 1.31)
Non-fatal stroke	108 (2.9)	0.89	111 (3.0)	0.92	0.97 (0.74; 1.26)
Hospitalisation for heart failure	117 (3.2)	0.96	163 (4.4)	1.36	0.71 (0.56; 0.90)
Secondary renal composite endpoint and its components					
Composite of kidney failure, sustained eGFR decline ≥ 40% or renal death	350 (9.5)	3.15	395 (10.8)	3.58	0.87 (0.76; 1.01) p = 0.0689 **
Kidney failure	46 (1.2)	0.40	62 (1.7)	0.54	0.72 (0.49;1.05)
Sustained eGFR decline ≥ 40%	338 (9.2)	3.04	385 (10.5)	3.49	0.87 (0.75; > 1.00)
Renal death	0	-	2 (< 0.1)	-	-
Secondary efficacy endpoints					
All-cause mortality	333 (9.0)	2.68	370 (10.1)	3.01	0.89 (0.77; 1.04) **
All-cause hospitalisation	1,573 (42.7)	16.91	1,605 (43.8)	17.52	0.97 (0.90; 1.04) **
Composite of kidney failure, sustained eGFR decline ≥ 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.
** 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



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 21%, reduced C_{max} by 19% and prolonged the time to reach C_{max} 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 ($t_{½}$) 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 2,827 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 3,683 patients who received finerenone in the FIGARO-DKD study, 52% of patients were 65 years and older, and 13% were 75 years and older.
In both studies, no overall differences in safety or efficacy were observed between these patients and younger patients.

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 [CLCR] 60 to < 90 mL/min) did not affect finerenone AUC and C_{max}.
Compared to patients with normal renal function (CLCR ≥ 90 mL/min), the effect of moderate (CLCR 30 to < 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).
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}. The C_{max} of a subject with a body weight of 50 kg was estimated to be 38% to 51% higher compared to a subject of 100 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 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.

In vivo 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.

A single dose of 20 mg finerenone also had no clinically relevant effect on AUC and C_{max} of the CYP2C8 probe substrate repaglinide. Thus, finerenone does not inhibit CYP2C8.

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 10 to 60 times that in humans. The dose free of findings provides a safety margin of about 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 26 times the $AUC_{unbound}$ in humans. A dose representing 17 times the $AUC_{unbound}$ in humans did not cause any tumours. Based on the known sensitivity of rodents to develop these tumours and the pharmacology-based mechanism at supratherapeutic 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 19 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 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for $AUC_{unbound}$. 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 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioural changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$. The increased locomotor activity in offspring may indicate a potential risk for the 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 21 times the human $AUC_{unbound}$. In addition, reduced ovarian weights were found at about 17 times the human $AUC_{unbound}$. No effects on female fertility and early embryonic development were found at 10 times the human $AUC_{unbound}$. Therefore, the findings in female rats are of little clinical relevance (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Croscarmellose sodium
Hypromellose 2910
Lactose monohydrate
Magnesium stearate
Sodium laurilsulfate

Tablet coating

Hypromellose 2910
Titanium dioxide
Talc

FIRIALTA 10 mg film coated-tablets
Iron oxide red (E 172)
FIRIALTA 20 mg film coated-tablets
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine 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 or 28 film-coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
Collaboration Hub, 1st Floor,
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8. REGISTRATION NUMBER(S)

Firialta® 10 mg film-coated tablets – 57/18.10/0242
Firialta® 20 mg film-coated tablets – 57/18.10/0243

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 March 2025

10. DATE OF REVISION OF THE TEXT

30 April 2026