SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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 of finerenone.

Excipient with known effect
Each film-coated tablet contains 45 mg of lactose (as monohydrate), see section 4.4.

Firialta 20 mg film-coated tablets

Each film-coated tablet contains 20 mg of finerenone.

Excipient with known effect
Each film-coated tablet contains 40 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) 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 (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.

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’.

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 study (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 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

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

Firialta 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 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 medicinal products 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 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 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 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 medicinal products
The risk for hypotension increases with concomitant use of multiple other antihypertensive medicinal products. 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 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 Firialta 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

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 (18.3%). See 'Description of 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 the pivotal phase III study FIDELIO-DKD (diabetic kidney disease). In this study 2,827 patients received finerenone (10 or 20 mg once daily) with a mean duration of treatment of 2.2 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	
Vascular disorders		Hypotension	
Skin and subcutaneous tissue disorders		Pruritus	
Investigations		Glomerular filtration rate decreased	Haemoglobin decreased

Description of selected adverse reactions

Hyperkalaemia
In the FIDELIO-DKD study, hyperkalaemia events were reported in 18.3% of finerenone-treated patients compared with 9.0% of placebo-treated patients. In patients treated with finerenone, the majority of hyperkalaemia events were mild to moderate and resolved. Serious events of hyperkalaemia were reported more frequently for finerenone (1.6%) than for placebo (0.4%). Serum potassium concentrations > 5.5 mmol/L and > 6.0 mmol/L were reported in 21.7% and 4.5% of finerenone-treated patients and in 9.8% and 1.4% of placebo-treated patients, respectively. Hyperkalaemia leading to permanent discontinuation in patients who received finerenone was 2.3% versus 0.9% in the placebo group. Hospitalisation due to hyperkalaemia in the finerenone group was 1.4% versus 0.3% in the placebo group.
An increase from baseline in mean serum potassium was observed in the first month of finerenone treatment compared to placebo and a maximum between-group difference of 0.23 mmol/L at month 4. The difference in serum potassium between finerenone and placebo remained stable thereafter.
For specific recommendations, refer to sections 4.2 and 4.4.

Hypotension
In the FIDELIO-DKD study, hypotension events were reported in 4.8% of finerenone-treated patients compared with 3.4% of placebo-treated patients. In patients treated with finerenone, the majority of hypotension events were mild or moderate and resolved. In one patient (<0.1%), finerenone treatment was permanently discontinued due to hypotension. Hospitalisation due to hypotension in the finerenone group was 0.2% versus 0.2% in the placebo group.
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.

Glomerular filtration rate (GFR) decreased
In the FIDELIO-DKD study, GFR decreased events were reported in 6.3% of finerenone-treated patients compared with 4.7% of placebo-treated patients. In patients treated with finerenone, the majority of GFR rate decreased events were mild or moderate and resolved. GFR rate decreased events leading to permanent discontinuation in patients who received finerenone were 0.2% versus 0.3% in the placebo group. Hospitalisation due to decreased GFR filtration rate in the finerenone group was 0.1% versus 0.1% in the placebo group.
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
After 4 months of treatment, finerenone was associated with a placebo-corrected absolute decrease in mean haemoglobin of 0.14 g/dL and mean haematocrit of 0.46%. Changes in haemoglobin and haematocrit were transient and reached comparable levels to those observed in the placebo-treated group after about 24 months. Anaemia was slightly increased in finerenone-treated patients (7.4%) compared with placebo-treated patients (6.7%). The frequency of serious events of anaemia was low and balanced (0.5% in finerenone-treated patients versus 0.7% in placebo-treated patients).

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 national reporting system.

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, a randomised, double-blind, placebo-controlled, multicentre phase III study 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% at month 4.

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 study investigated the effect of finerenone compared to placebo on kidney and cardiovascular (CV) outcomes in adult patients with CKD and T2D. 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 m^2, serum potassium ≤ 4.8 mmol/L at screening, and were required to be receiving standard of care, including a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). 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.

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 m^2 over at least 4 weeks), a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death. The key secondary endpoint was a composite of time to first occurrence of CV death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalisation for heart failure.

A total of 5,674 patients were randomised to receive either finerenone (N = 2,833) or placebo (N = 2,841) 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, 30% 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 44.3 mL/min/1.73 m^2, with 55% of patients having an eGFR < 45 mL/min/1.73 m^2, median UACR was 852 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 at baseline, respectively. At baseline, almost all patients were on ACEi (34%) or ARB (66%), and 97% of patients used one or more antidiabetic medications (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). The other most frequent medications taken at baseline were statins (74%) and calcium channel blockers (63%).
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). For the secondary endpoint of change in UACR from baseline to month 4, a relative reduction of 31.2% was observed in the finerenone group compared to placebo. The treatment effect for the primary and key secondary endpoints was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure (BP) and HbA1c at baseline.

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) ****
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.

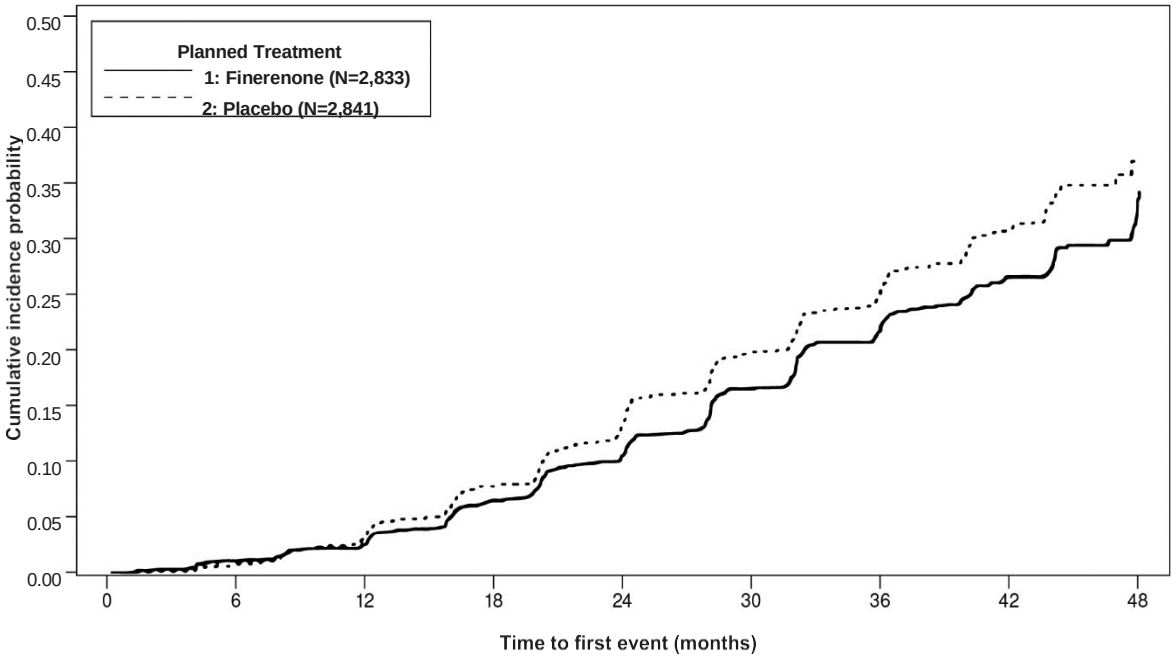
**** p = not statistically significant after adjustment for multiplicity

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



Number of subjects at risk

1	2833	2705	2607	2397	1808	1274	787	441	83
2	2841	2724	2586	2379	1759	1248	792	453	82

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Firialta in one or more subsets of the paediatric population in treatment of chronic kidney disease (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 exposure 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% 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. No overall differences in safety or efficacy were observed between these patients and younger patients.
In a phase I study (N = 48) elderly patients (≥ 65 years of age) exhibited higher finerenone plasma concentrations than younger patients (≤ 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}. The C_{max} of a subject with a body weight of 50 kg was estimated to be 43% to 51% higher compared to a subject of 100 kg. Dose adaptation based on body weight is not warranted (see section 4.2).

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.

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.

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

Cellulose, microcrystalline
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 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 size of 28 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. DATE OF REVISION OF TEXT

23/06/202