Date: 1 February 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Kerendia

International non-proprietary name: finerenone
Pharmaceutical form: film-coated tablets
Dosage strengths: 10 mg and 20 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Bayer (Schweiz) AG
Marketing Authorisation No.: 68130
Decision and Decision date: approved on 26 November 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AEs	Adverse events
AKI	Acute kidney injury
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARB	Angiotensin receptor blockers
ARR	Absolute risk reduction
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BSEP	Bile salt export pump
CI	Confidence interval
CIF	Cumulative incidence function
CKD	Chronic kidney disease
CL/F	Apparent clearance
Cmax	Maximum observed plasma/serum concentration of drug
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DDI	Drug-drug interaction
DKD	Diabetic kidney disease
DN	Diabetic nephropathy
EC50	Half-maximal effective concentration
EC90	90% maximal effective concentration
eGFR	Estimated glomerular filtration rate
eGFR-EPI	Estimated glomerular filtration rate calculated using the chronic kidney disease epidemiology collaboration formula
Emax	Maximum effect
ERA	Environmental Risk Assessment
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
F	Relative bioavailability
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A_{1C}
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
hHF	hospitalisation for heart failure
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MACEs	Major adverse cardiovascular events
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxin extrusion

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Max	Maximum
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
Min	Minimum
MP	Metabolite/parent
MRAs	Mineralocorticoid receptor antagonists
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OEs	Outcome events
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamics
Pgp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PPI	Proton pump inhibitor
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RAS	Renin-angiotensin system
RMP	Risk Management Plan
SAF	Safety analysis population
SGLT2	Sodium–glucose cotransporter 2
SGLT2i	Sodium–glucose cotransporter 2 inhibitor
SwissPAR	Swiss Public Assessment Report
T2DM	Type 2 diabetes mellitus
TEAEs	Treatment-emergent adverse events
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UACR	Urine albumin-to-creatinine ratio
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
Vc/F	Apparent central volume of distribution
Vss	Volume of distribution at steady state

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance finerenone of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Singapore and Switzerland.
The ACCESS NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

For aspects of the evaluation not covered in this SwissPAR, please refer to the publicly available assessment reports for Kerendia issued by the regulatory authorities HSA and TGA (see https://www.hsa.gov.sg/therapeutic-products/register/summary-reports-of-benefit-risk-assessment and https://www.tga.gov.au/ws-auspar

2.2 Indication and Dosage

2.2.1 Requested Indication

Kerendia is indicated to delay progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease and type 2 diabetes mellitus.

2.2.2 Approved Indication

Kerendia is indicated to delay progression of chronic kidney disease in adult patients with type 2 diabetes mellitus (see "Dosage/Administration" and "Clinical efficacy" sections).
For study outcomes regarding the effects on cardiovascular events, see "Clinical efficacy" section.

2.2.3 Requested Dosage

The recommended target dose of Kerendia is 20 mg once daily (equivalent to the maximum daily dose).
Initiation of therapy
Initiation of therapy with Kerendia is recommended when the serum potassium level is ≤ 4.8 mmol/L.
If the serum potassium level is > 4.8 to 5.0 mmol/L, treatment with Kerendia may be considered depending on patient characteristics and serum potassium levels, with additional serum potassium monitoring within the first 4 weeks.
If the serum potassium level is > 5.0 mmol/L, treatment with Kerendia is not recommended.
The estimated glomerular filtration rate (eGFR) is measured to determine the starting dose. The starting dose of Kerendia is:

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

Initiation of therapy with Kerendia is not recommended in patients with eGFR < 25 mL/min/1.73 m^2 due to the limited clinical experience.

Maintenance therapy
Four weeks after initiation, restart or up-titration of treatment with Kerendia, serum potassium and eGFR must be remeasured. Thereafter, measurement of serum potassium should be repeated periodically and as needed based on patient characteristics and the serum potassium level.

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Continuation (4 weeks after initiation, restart or up-titration) of treatment with Kerendia and dose adjustment

Serum potassium (mmol/L)	Dosage of Kerendia (starting from week 5)
≤ 4.8	Maintain dosage of 20 mg once daily. For patients on a dosage of 10 mg once daily, increase the dosage to 20 mg once daily if eGFR has not decreased by > 30% compared to the previous measurement.
> 4.8-5.5	Maintain dosage.
> 5.5	Withhold dosing with Kerendia. Resume dosing at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.

(For full dosage recommendations, see *information for healthcare professionals*)

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	1 December 2020
Formal control completed	30 December 2020
List of Questions (LoQ)	29 April 2021
Answers to LoQ	28 June 2021
Predecision	23 August 2021
Answers to Predecision	7 September 2021
Labelling corrections	26 October 2021
Answers to Labelling corrections	2 November 2021
Final Decision	26 November 2021
Decision	approval

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3 Medical Context

Chronic kidney disease (CKD) is defined as persistent reduction in estimated glomerular filtration rate (eGFR), persistent albuminuria, or both. Reduced eGFR and albuminuria independently and additively increase all-cause and cardiovascular (CV) mortality. In patients with type 2 diabetes mellitus (T2DM), CKD frequently leads to end-stage kidney disease (ESKD) with a 5-year survival rate of less than 50% in Switzerland. Apart from an increased risk for CKD, patients with T2DM also face a greater risk for major adverse CV events (MACE).

The first drugs approved for nephron protection were inhibitors of angiotensin-converting enzyme (ACEI) and angiotensin receptor blockers (ARBs). However, long-term outcomes have remained unsatisfactory. More recently, inhibitors of the sodium–glucose cotransporter 2 (SGLT2i) have been shown to improve long-term outcomes of kidney function in patients with T2DM. Likewise, SGLT2i as well as glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to reduce MACE in patients with T2DM.

However, there is a need for further improvement of renal and CV outcomes of patients with T2DM.

In view of counteracting alternative pathophysiological mechanisms (e.g., renal fibrosis caused by excessive aldosterone secretion), mineralocorticoid receptor antagonists (MRAs) may represent a useful supplement to the drugs mentioned above in the treatment of CKD and CV disease in patients with T2DM.

4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME
Biopharmaceutical Development and Absorption

Finerenone was classified as a BCS II drug (low solubility, high permeability). The absolute bioavailability of finerenone was 43.5 %. The administration of finerenone with a high-fat high-calorie meal mainly caused a delay in the finerenone absorption. The median tmax was prolonged from 0.75 h to 2.5 h, whereas Cmax was 18.7% lower after fed administration. The finerenone AUC was 21% higher after fed administration.

After the tablet was crushed and resuspended in applesauce, the finerenone Cmax and AUC were 11% and 18.4% lower, respectively, compared to the administration of the intact tablet. The data support the recommendations related to the intake of finerenone in the approved Information for Healthcare Professionals included in Appendix 8.1 of the SwissPAR.

Dose Proportionality
A dose proportional increase in the finerenone exposures was observed between 1.25 mg and 80 mg.

Pharmacokinetics after multiple Dosing
In agreement with its short half-life, finerenone exhibited a low degree of accumulation after multiple dosing. The mean accumulation ratio for AUC was 1.21 to 1.33 after twice daily (BID) dosing and 1.1 after once daily (QD) dosing. The linearity index was 1.2, 1.32 and 1.1 after 10 mg BID, 20 mg BID and 40 mg QD, respectively, indicating a minor degree of time dependency. Finerenone reached its steady state on the first day after BID or QD dosing.

Due to their longer half-life, the accumulation after multiple dosing was higher for the metabolites, but in all cases the mean accumulation was < 2-fold. The metabolites reached their steady state within 1 day of BID dosing and within 2 days of QD dosing.

Distribution

The finerenone Vss after intravenous administration was 52.6 L. The mean blood to plasma ratio based on AUCinf of total radioactivity after administration of a ^{14}C-labelled dose was 0.65, indicating that finerenone mainly distributes in plasma and not in red blood cells. The *in vitro* blood to plasma ratio was approximately 1. The *in vitro* blood to plasma ratios of M1, M2 and M3 were 0.61, 0.71 and 0.75, respectively.

The *in vitro* finerenone fraction unbound was 8.33% at concentrations up to 4289 ng/mL. At higher finerenone concentrations the fraction unbound increased, indicating saturation of the plasma protein binding at far supratherapeutic exposure. The main binding site of finerenone was serum albumin.

The *in vitro* fraction unbound of M1a, M2a and M3a was 5.82%, 17.4% and 67.8%, respectively.

The mean *ex vivo* fractions unbound of finerenone, M1, M2 and M3 were approximately 10%, 6%, 15% and 82%, respectively. Renal impairment of all degrees had no major impact on the plasma protein binding of finerenone or its metabolites. The *ex vivo* fraction unbound of finerenone was 12.2% higher in subjects with moderate hepatic impairment compared to healthy controls.

Metabolism - In vitro Data

Finerenone was mainly metabolised by CYP3A4 and, to a lesser extent, by CYP1A1, 2C8, 3A5 and 3A7. Finerenone was not a substrate for UGTs.

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Metabolism - Clinical Data

Finerenone was almost exclusively cleared by oxidative biotransformation via naphthyridine derivatives (M1, M2, and M3) and dihydrodiol derivatives. M1, M2 and M3 exhibited axial chirality as pairs (atropisomers), each consisting of an "a"- and a "b"-series. In human plasma, the “a” series of all three metabolites was the predominant species.

After administration of a ^{14}C-labelled dose, finerenone covered 7.1% of total radioactivity AUC, M1 represented 48.9% (=> most abundant compound in plasma), M2 represented 21.5%, M3 represented 9.0% of the total radioactivity AUC in plasma. About 90% of the total radioactivity in plasma was assigned to finerenone and its metabolites.

The median tmax values for M1, M2 and M3 after oral administration of finerenone were 1.0 h, 4.0 h and 6.0 h, respectively. The metabolites are not pharmacologically active.

Based on “cold” data, the metabolite/parent (MP) ratios after i.v. and oral administration were as follows:

- M1: 2.99 and 6.87
- M2: 1.39 and 4.03
- M3: 0.22 and 1.11

The MP ratio was consistently higher after oral administration, indicating a substantial degree of first pass metabolism. This is in agreement with the relatively low absolute bioavailability of finerenone. Because of the different degrees of accumulation, the MP ratio was slightly higher after multiple dosing compared to single dosing.

After administration of a ^{14}C-labelled dose, finerenone accounted for 0.825% of dose excreted in urine. The naphthyridine carboxylic acid metabolite M3 accounted for the majority of the excreted radioactivity in urine, at 46.3% of the administered dose. The major plasma metabolite M1 was not detected in urine. Overall, 87.1% of the radioactivity excreted in urine samples could be assigned to finerenone and its metabolites.

In faeces, finerenone accounted for 0.184% of the radioactive dose. M5 was the main component accounting for 9.40% of the administered dose. Overall, 81.0% of the radioactivity excreted in faeces samples could be assigned to finerenone and its metabolites.

Elimination

After administration of a single ^{14}C-labelled dose, 79.6% and 21.2% of the radioactive dose were excreted in urine and faeces, respectively. Most of the radioactivity in urine and faeces was excreted within 48 h and 96 h post-dose, respectively.

The finerenone plasma clearance after intravenous administration was 22.3 L/h. Its half-life was between 2 h and 3 h. Less than 2% and less than 1% of the administered dose were excreted as unchanged finerenone in urine after intravenous and oral administration, respectively.

The half-lives of M1, M2 and M3 were 8.4 h, 6.3 h and 5.9 h, respectively.

While the urinary excretion of M1 was minimal, 14% and 33.7% of the administered finerenone dose were excreted as M2 and M3 in urine, respectively.

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Special Populations / Intrinsic Factors

In a dedicated study in healthy subjects, age and gender had no major impact on the exposure of finerenone, M1, M2, or M3. The non-significant impact of age and gender on finerenone exposures was also supported by a pop PK analysis including several Phase 1 studies and a pop PK analysis including patients with type 2 diabetes and chronic kidney disease.

There were no major differences in finerenone exposures between healthy Asians and Caucasians after accounting for body weight. This was also the case for patients with diabetic nephropathy (DN) and for patients with diabetic kidney disease (DKD).

Mild, moderate or severe renal impairment had no major impact on finerenone Cmax and AUC. Cmax was barely affected and there was a 1.36-fold increase in the finerenone AUC in subjects with severe renal impairment compared to healthy controls.

Mild or moderate hepatic impairment had no major effect on total and unbound finerenone exposures. The largest effects observed were 1.38-fold and 1.55-fold increases in the total and unbound finerenone AUC in subjects with moderate hepatic impairment.

Subjects with severe hepatic impairment were not investigated.

Overall, mild or moderate hepatic impairment had a small effect on the exposures of finerenone and its metabolites.

Several other demographic and disease-related factors, including age, gender, hepatic and renal function were investigated in the pop PK analysis for DKD patients. The range of the continuous covariates in the dataset was sufficiently wide to detect potential covariate effects. The DKD patient population was relatively old (mean age 65 years, only 34 patients between 18 and 44 years). Most patients had mild hepatic impairment (Child Pugh A). The dataset included 114 patients with moderate hepatic impairment (Child Pugh B) and no patients with severe hepatic impairment. The majority of the patients had an eGFR between 25 and ≤ 45 mL/min at screening

The final pop PK model was a linear two-compartment model. It described the finerenone plasma concentration data reasonably well.

The final pop PK model included the following covariate relationships:

- Body weight on Vc/F
- Creatinine on CL/F and F
- Time varying eGFR-EPI on CL/F and F
- GGT on CL/F
- Height on CL/F and F
- Korean origin on Vc/F
- SGLT-2 inhibitors on CL/F and F
- Smoking on CL/F and F
- Co-administration of CYP3A4 inhibitors on CL/F and F

The impact of these covariates on finerenone exposures was low.
The finerenone PK was similar in healthy subjects, DN and DKD patients.

The data support the dosing recommendations for special patient populations in the approved information for healthcare professionals included in Appendix 8.1 of the SwissPAR.

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Interactions

EFFECT OF OTHER DRUGS ON FINERENONE

In vitro Data

As mentioned above, finerenone was mainly metabolised by CYP3A4. Finerenone was a substrate for Pgp, but not for BCRP, OATP1B1, OATP1B3 or OCT1.

Clinical Data

The interaction potential of finerenone as a victim was evaluated for the following perpetrators in clinical interaction studies: omeprazole (proton pump inhibitor PPI), Maalox (antacid), erythromycin (moderate CYP3A4 inhibitor, OATP1B1 and 1B3 inhibitor), verapamil (moderate CYP3A4 inhibitor, Pgp inhibitor), and gemfibrozil (strong CYP2C8 inhibitor, OATP1B1 and 1B3 inhibitor).

The effect of itraconazole (strong CYP3A4 inhibitor), clarithromycin (strong CYP3A4 Inhibitor), fluvoxamine (weak/moderate CYP3A4 inhibitor), efavirenz 600 mg QD (moderate CYP3A4 inducer) and rifampicin (strong CYP3A4 inducer) on finerenone exposures was assessed by physiologically based pharmacokinetic (PBPK) simulations.

The finerenone PBPK model used to evaluate the effect of strong CYP3A4 inhibitors and CYP3A4 inducers on finerenone exposures was built with the data of several studies in healthy subjects. A different set of studies in healthy subjects was used for model verification. Apart from its use to predict the impact of perpetrators on finerenone exposures, it was also used to predict the finerenone exposures in subjects/DKD patients with impaired renal function. The model predicted the finerenone exposure quite well in all stages of development and can therefore be regarded as qualified for the prediction of interactions.

For this purpose, the finerenone PBPK model was coupled with existing, qualified perpetrator PBPK models. The combined model was successfully verified by the simulation of the clinical interaction studies with erythromycin and verapamil.

Only the co-administration of moderate or strong CYP3A4 inhibitors and CYP3A4 resulted in clinically relevant changes of the finerenone exposures

The data are summarised in Section 8 of the approved information for healthcare professionals included in Appendix 8.1 of the SwissPAR and support the dosing recommendations for the co-administration of finerenone with CYP3A4 inhibitors or inducers.

EFFECT OF FINERENONE ON OTHER DRUGS

In vitro Data

Inhibition of CYPs

The static drug-drug interaction (DDI) risk assessment indicated a risk for the inhibition of intestinal CYP3A4 and, to a lesser extent and depending on the model applied, CYP2C8 by finerenone. No *in vivo* CYP inhibition was predicted for M1a, M2a or M3a.

Induction of CYPs

Finerenone had the potential to induce all investigated CYPs (CYP1A2, 3A4, 2B6 and 2C19). The largest effect was observed for CYP3A4, followed by CYP2B6. A weak to moderate induction of

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CYP3A4 was predicted for finerenone. Similar results were obtained for M1a. M2a induced CYP3A4 and 2B6, but not CYP1A2 or 2C19. No CYP induction was observed for M3a. A weak to moderate induction of CYP3A4 was predicted for M1a and M2a.

Inhibition of Transporters

The static DDI risk assessment indicated a risk for the inhibition of BCRP and OATP1B1 by finerenone. No *in vivo* inhibition was expected for Pgp, BSEP, MATE1, MATE2K, OATP1B3, OAT1, OAT3, OCT1 and OCT2. No *in vivo* inhibition of the transporters mentioned above was expected for M1a and M2a.

The static DDI risk assessment indicated a risk for the inhibition of OATP1B3 by M3a. The *in vivo* inhibition of the other transporters by M3a appeared unlikely.

Other *in vitro* Data

Neither finerenone nor M1a+b, M2a, M3a inhibited UGT1A1, 1A4, 1A6, 1A9, 2B4 or 2B7. Finerenone did not inhibit the metabolism of SGLT2 inhibitors *in vitro*.

Clinical Data

The interaction potential of finerenone as a perpetrator was assessed for the following victims in clinical interaction studies: midazolam (CYP3A4 substrate), repaglinide (CYP2C8 substrate), warfarin (S-enantiomer CYP2C9 substrate, R-enantiomer CYP3A4 substrate), digoxin (Pgp substrate), and rosuvastatin (BCRP and OATP substrate).

The potentially relevant induction and inhibition of CYP3A4 *in vitro* by finerenone and/or its metabolites resulted in a “zero effect” in vivo. The much weaker *in vitro* effect on CYP2C8 was confirmed *in vivo*.

Finerenone and its metabolites did not inhibit Pgp at clinically relevant concentrations *in vitro*. This was confirmed by the clinical interaction study. Based on the available clinical data, the interaction potential of finerenone as a perpetrator appeared to be low.

The data are summarised in Section 8 of the approved information for healthcare professionals included in Appendix 8.1 of the SwissPAR and support the dosing recommendations for the co-administration of finerenone and the CYP/transporter substrates described above.

Pharmacodynamics

Safety

Finerenone caused no QTc prolongation after administration of single doses of 20 mg and 80 mg. The active control moxifloxacin showed the expected effect, i.e. assay sensitivity was formally demonstrated.

No QTcF or QTcI values > 450 ms were observed after both finerenone doses.

No QTcF or QTcI changes from baseline > 30 ms were observed after both finerenone doses.

Finerenone had no effect on QRS, PR, ventricular rate or RR.

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As no substantial accumulation of finerenone or its metabolites was observed after multiple dosing and the finerenone exposure was similar in healthy subjects and patients, the administration of single doses in the tQT study was acceptable. Supratherapeutic exposure was achieved.

Relationships between Plasma Concentration and Effect

Efficacy – Renal Composite Endpoint

Cox proportional hazard analyses were conducted to investigate the relationship between finerenone exposure and the renal and cardiovascular (CV) composite endpoints.

The final model described the data reasonably well.

The maximum decrease in the hazard of experiencing a renal event was estimated to be 36.1%, the half-maximal effective concentration (EC50) was 0.166 ng/mL. For a “typical subject”, the Cmax after multiple dosing was 109-fold higher than the EC90 after 20 mg finerenone QD. The simulated duration above the EC90 within a 24 h dosing interval was 15.5 h after 10 mg finerenone QD at steady-state and 18.3 h after 20 mg finerenone QD at steady-state.

The final model included the following prognostic factors (covariates):

- Urine albumin-to-creatinine ratio (UACR) at baseline (=> increasing hazard of a renal event with increasing UACR)
- Estimated glomerular filtration rate calculated using the ’CKD epidemiology collaboration’ formula (eGFR-EPI) at baseline (=> decreasing hazard with increasing eGFR)
- Body mass index (BMI) at baseline (=> decreasing hazard with increasing BMI)
- Age at baseline (=> decreasing hazard with increasing age)
- Race/Ethnicity (=> Black/African American: 102% increase in the hazard versus all other ethnicities/races and All Asian ethnicities, except Japanese: 20.3% increase in the hazard versus all other ethnicities/races)
- SGLT-2 inhibitor use for ≥ 50% of the at-risk period (=> 50.7% decrease in the hazard versus no or < 50% SGLT-2 inhibitor use during the at-risk period)
- GLP-1 agonist use in the at-risk period (=> 34.2% decrease in the hazard versus no GLP-1 agonist use in the at-risk period)
- Child-Pugh Score (Child-Pugh B: 69.9% increase in the hazard versus likely Child-Pugh A)

Apart from the estimated effects of BMI and age, the results were plausible. The reason for the unexpected effects of BMI and age is unknown.

Efficacy – CV Composite Endpoint

The final model included the following prognostic factors (covariates):

- Age at baseline (=> increasing hazard of a CV event with increasing age)
- UACR at baseline (=>increasing hazard with increasing UACR)
- Body weight at baseline (=> increasing hazard with increasing weight)
- eGFR-EPI, time varying (=> the overall model prediction was a decreasing hazard with increasing eGFR, resulting in the “misfit” of the data described above)
- Haemoglobin A1c (HbA1c) at baseline (=> increasing hazard with increasing HbA1c values)
- Child-Pugh Score (=> Child-Pugh B: 59.8% increase in the hazard versus likely Child-Pugh A)
- Race/Ethnicity (=> East Asia (Japanese + Korean + Chinese): 38.8% decrease in the hazard, all other races/ethnicities, except White: 12.1% decrease in the hazard versus White)

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- Weak CYP inhibitor use for >0-50% of the at-risk period (=>92.7% increase in the hazard versus no CYP3A4 inhibitor use)
- Weak CYP inhibitor use for >50% of the at-risk period (=> 39.6% increase in the hazard versus no CYP3A4 inhibitor use)
- Moderate, Strong and Unclassified CYP3A4 inhibitor use >0% of the at-risk period combined (=>43.8% increase in the hazard versus no CYP3A4 inhibitor use)

The effects of the prognostic factors were all plausible. The effect of the CYP3A4 inhibitors was deemed to be likely due to the underlying disease for which they were administered.

Safety

The relationship between serum potassium levels and finerenone AUCtau,md was adequately described by a turnover model. The model estimated a maximum increase in serum potassium of 9.95% under finerenone treatment and a slower disease progression rate for finerenone compared to placebo (0.412% versus 0.161% per year increase in serum potassium, respectively, for patients with baseline serum potassium of 4.4 mmol/L and UACR0 of 800 mg/g). The disease progression rate was also affected by baseline serum potassium (16% faster progression with each 0.1 mmol/L increase in baseline serum potassium) and baseline UACR (11.4% faster progression with each 100 mg/g increase of baseline UACR).

The final model included the following additional covariate relationships:

- Baseline eGFR-EPI on baseline serum potassium (=> higher baseline serum potassium with lower eGFR-EPI)
- Baseline eGFR-EPI on the maximum effect (=> higher Emax (increase of serum potassium) with lower eGFR-EPI).
- Baseline UACR on Emax (=> higher Emax with higher UACR).
- Sex on Emax (=> 14.3% lower Emax in females).
- Japanese ethnicity on baseline serum potassium (=> 3.62% lower) and standard deviation of residual error (=>13% lower).

6.2 Dose Finding and Dose Recommendation

The following set of Phase 2 studies contributed to the dose finding.

	ARTS (N=65 Part A / N=392 Part B)	ARTS-HF (N=1066)	ARTS-DN (N=823)
Primary Endpoint	Change in serum potassium over 4 weeks	Proportion of patients with >30% decline in NT-proBNP	Change in UACR
Treat-ment	Finerenone 2.5, 5, 10 mg OD (Part A/B) 5 mg BID (Part B only) Placebo (Part A/B) Open-label spironolactone 25 or 50 mg QD (Part B)	Finerenone 2.5, 5, 7.5, 10, 15 mg QD up-titrated to 5, 10, 15, 20, 20 mg QD on day 30 if serum potassium ≤ 5mmol/l Eplerenone 25 mg QOD up-titrated to 25 mg QD on day 30 and 50 mg QD on day 60 if serum potassium ≤ 5mmol/l	Finerenone 1.25, 2.5, 5, 7.5, 10, 15, and 20 mg QD Placebo
Duration	4 weeks	3 months	3 months
Study popu-lation	HFrEF and mild or moderate CKD *Part A: eGFR 60-90 mL/min/1.73 m²* *Part B: eGFR 30-60 mL/min/1.73 m²*	HFrEF and CKD ± T2DM *With T2DM: eGFR ≥30 mL/min/1.73 m²* *No T2DM: eGFR 30-60 mL/min/1.73 m²*	CKD and T2DM receiving ACEI/ARB *UACR ≥ 30 mg/g and* *eGFR >30 mL/min/1.73 m²*

Modified from Ref. [19]

The **ARTS** study examined finerenone doses of 2.5 mg QD, 5 mg QD, 5 mg BID, and 10 mg QD in a population of patients with chronic heart failure and reduced ejection fraction (HFrEF) who had mild

(Part A with 65 patients) and moderate (Part B with 393 patients) impairment of renal function. The difference from placebo in the change of serum potassium was statistically significant exclusively for finerenone 10 mg QD. At the same time, the increase in serum potassium caused by any dose of finerenone was smaller than in the active comparator (spironolactone) arm.

The international **ARTS-DN** study examined the nephroprotective effect of finerenone (1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg, all QD) in addition to treatment with ACEI/ARB in 823 patients with T2DM and diabetic nephropathy. The primary efficacy analysis ($UACR_{Day\ 90}/UACR_{Baseline}$) demonstrated a dose-dependent effect of finerenone. The treatment difference from the placebo group reached statistical significance ($p < 0.05$) for finerenone doses of 7.5 mg QD and above. The reductions in UACR were 25% and 38% for 10 mg QD and 20 mg QD, respectively.

An analogous study (**ARTS-DN JAPAN**) in 96 Japanese patients confirmed a difference from the placebo group for the highest dose of finerenone (20 mg OD).

The large (1066 patients), international **ARTS-HF** study examined the treatment effect of finerenone (2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg, all QD) in a population with worsening chronic HFrEF and moderate CKD, with or without T2DM. The study included an active comparator (eplerenone) arm. None of the finerenone doses was superior to eplerenone for the primary endpoint (percentage of subjects achieving an N-terminal pro-B-type natriuretic peptide [NT-proBNP] reduction from baseline to Day 90 of >30%: 30.9% [2.5-5 mg QD] and 38.8% [10-20 mg QD] versus 37.2%, respectively). There appeared to be a beneficial effect of finerenone (in particular of the 20 mg QD dose) on various categories of hospitalisation and mortality.

The regional **ARTS-HF Japan** trial enrolling 72 Japanese patients observed a numerical increase in the responder rate as compared with eplerenone for finerenone doses of 10 mg, 15 mg, and 20 mg QD, but failed to corroborate the findings from the ARTS-HF trial for hospitalisations and mortality.

Considering the data from all Phase 2 trials, finerenone appeared to be safe up to a daily dose of 20 mg in populations with moderate CKD and/or HFrEF. The efficacy data suggested an optimal finerenone dose for patients with CKD in the range from 10 mg to 20 mg QD.

6.3 Efficacy

The demonstration of efficacy for finerenone in the requested indication is based on the data from the pivotal Phase 3 study FIDELIO-DKD carried out in patients with T2DM and CKD who already received treatment with a drug targeting the renin-angiotensin system.

The FIDELIO-DKD trial was a large (5674 patients [68.9% males]), multi-centre (1024 sites across 48 countries), randomised, placebo-controlled, double-blinded Phase 3 study aimed to demonstrate efficacy and safety of finerenone in the treatment of patients with CKD and T2DM. In addition, the study investigated the effect of finerenone on the cardiovascular risk in this population.

The trial enrolled patients aged ≥ 18 years with T2DM and the clinical diagnosis of CKD who already received treatment with an ACEI or ARB. Serum potassium level had to be ≤ 4.8 mmol.

Study participants received treatment with either finerenone (10 mg or 20 mg) or placebo on top of standard of care for T2DM (~97% at baseline) and other co-morbidities (e.g. statin [~74% at baseline], beta-blocker [~52% at baseline], ARB [~65% at baseline], ACEI [~34% at baseline], and diuretic [~56% at baseline]). The median treatment duration was of 27 months amounting to a total exposure of 6346 patient-years (finerenone) and 6431 patient-years (placebo) in the two treatment arms.

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Primary and key secondary endpoints were as follows:

Primary	Time to the 1st occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥ 40% from baseline for ≥4 weeks, or renal death.
Secondary	Time to first occurrence of the following CV composite endpoint: cardiovascular (CV) death or non-fatal CV events (i.e. myocardial infarction, stroke, or hospitalization for HF) Time to all-cause mortality Time to all-cause hospitalization Change in UACR from baseline to Month 4 Time to first occurrence of the following renal composite endpoint: onset of kidney failure, a sustained decrease in eGFR of ≥ 57% from baseline over at least 4 weeks or renal death

Confirmatory statistics were performed in a pre-planned sequential design (hierarchical testing) using the weighted Bonferroni-Holm procedure for the primary and key secondary efficacy endpoints. The sequence had to be stopped at the level of all-cause mortality, meaning that the results for down-stream secondary endpoints are to be considered exploratory.

There was no clinically meaningful imbalance between treatment arms in patient demographics (age [median ~66 years], sex, representation of regions, race and ethnicity) and other relevant baseline characteristics, including a history of cardiovascular disease (CVD) (46% vs. 45.8%) and the use of comedications. The median HbA_{1C} at baseline was ~7.7%. With a median T2DM duration of ~16 years, >45% of the enrolled study participants had diabetic retinopathy, and almost 2/3 received insulin treatment. Only tiny fractions received treatment with SGLT2 inhibitors (~4.5%) and GLP-1 receptor agonists (~7%), respectively.

The study population was representative of a target population with CKD: a) the median eGFR was 43 ml/min/1.73m^2, b) nearly 90% of the patients had stage 3a or higher severe impairment of renal function (i.e. eGFR <60 ml/min/1.73m^2), and c) the geometric mean of the UACR was ~800 mg/g with a marginal imbalance between the treatment arms (798.79 mg/g [finerenone] vs. 814.73 mg/g [placebo]).

The FIDELIO-DKD study was well planned and conducted with a negligible discontinuation rate (99.7% completed the study in both treatment arms). A total of 1623 subjects (822 [29.0%] in the finerenone arm and 801 [28.2%] in the placebo arm did not complete the randomised treatment primarily due to adverse events (AEs) or outcome events (10.9% vs. 10.3%), withdrawal by the subject (5.5% vs. 5.9%), physicians' decision (5.2% vs. 3.8%), and death (4.6% vs. 5.5%).

Results of the FIDELIO-DKD study for the primary endpoint (composite of kidney failure, sustained decrease in eGFR ≥40%, or renal death) endorse superiority of finerenone versus placebo with regard to the progression of DKD: primary endpoint events occurred in 504 subjects (17.8%; 7.59 events per 100 patient-years) in the finerenone arm versus 600 subjects (21.1%, 9.08 events per 100 patient-years) in the placebo arm (hazard ratio (HR) [95% CI]: 0.825 [0.732 - 0.928]; p<0.0001). The absolute risk reduction (ARR) for the primary endpoint was 3.4%. This beneficial effect became apparent in the Kaplan-Meier curves for the cumulative incidence function (CIF), with a delay of ≥12 months, and persisted throughout the trial thereafter. All components apart from renal death (too few events [2 vs. 2]) contributed to the beneficial effect on the composite primary endpoint.

	Finerenone N = 2833 n (%)	**Placebo** N = 2841 n (%)	**Finerenone** n/100 p-yrs (95% CI)	**Placebo** n/100 p-yrs (95% CI)	**HR** (95% CI)
Number of subjects with a renal composite endpoint	**504 (17.8%)**	**600 (21.1%)**	**7.59 (6.94;8.27)**	**9.08 (8.37;9.82)**	**0.825 [0.732; 0.928]**
Components:					
Kidney failure	208 (7.3%)	235 (8.3%)	2.99 (2.60;3.41)	3.39 (2.97;3.83)	0.869 [0.721; 1.048]
ESRD	119 (4.2%)	139 (4.9%)	1.60 (1.33;1.90)	1.87 (1.57;2.20)	0.858 [0.672; 1.096]
Sustained decrease in eGFR to <15 mL/min	167 (5.9%)	199 (7.0%)	2.40 (2.05;2.78)	2.87 (2.48;3.28)	0.824 [0.671; 1.013]
Sustained decrease in eGFR ≥40% (relative to baseline)	479 (16.9%)	577 (20.3%)	7.21 (6.58;7.87)	8.73 (8.03;9.46)	0.815 [0.722; 0.920]

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A set of sensitivity analyses supported the robustness of the findings for the primary endpoint.

The results for the primary endpoint were largely consistent across subgroups (point estimates for HR mostly <1), but some findings suggested heterogeneity, as briefly summarised in the table below.

Subgroup factor	Subgroup level	HR [95% CI]	Interaction p-value
History of CVD	Present Absent	0.70 [0.58-0.84] 0.94 [0.80-1.09]	**0.0160**
Baseline BMI [kg/m^2]	< 30 ≥ 30	0.68 [0.58_0.81] 0.98 [0.83-1.17]	**0.0028**
	<20 20 - <25 25 - <30 30 - <35 ≥35	0.96 [0.28-3.33] 0.80 [0.59-1.07] 0.63 [0.51-0.78] 0.87 [0.70-1.09] 1.16 [0.90-1.49]	**0.0091**
Baseline waist circumference	normal increased substantially increased	0.84 [0.62-1.13] 0.60 [0.46-0.79] 0.91 [0.79-1.06]	**0.0274**

The results of the FIDELIO-DKD study for the key secondary endpoint (composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalisation for HF [hHF]) support superiority of finerenone treatment versus placebo with regard to the CV outcomes (HR [95 CI]: 0.860 [0.747-0.989]). The beneficial effect was driven by all components of the secondary endpoint except for non-fatal strokes (HR [95 CI]: 1.027 [0.765-1.380]) and occurred early on.

	Finerenone N = 2833 n (%)	Placebo N = 2841 n (%)	Finerenone n/100 p-yrs (95% CI)	Placebo n/100 p-yrs (95% CI)	HR (95% CI)	p-value
CV composite	**367 (13.0%)**	**420 (14.8%)**	**5.11 (4.60;5.64)**	**5.92 (5.37;6.50)**	**0.860 [0.747; 0.989]**	**0.0339**
Components:						
CV death	128 (4.5%)	150 (5.3%)	1.69 (1.41;2.00)	1.99 (1.68;2.32)	0.855 [0.675; 1.083]	0.1927
Non-fatal MI	70 (2.5%)	87 (3.1%)	0.94 (0.73;1.17)	1.17 (0.94;1.43)	0.796 [0.581; 1.090]	0.1540
Non-fatal stroke	90 (3.2%)	87 (3.1%)	1.21 (0.97;1.47)	1.18 (0.94;1.44)	1.027 [0.765; 1.380]	0.8579
Hospitalization due to heart failure	139 (4.9%)	162 (5.7%)	1.89 (1.59;2.21)	2.21 (1.89;2.57)	0.857 [0.683; 1.076]	0.1821

The ARR based on the Kaplan-Meier (KM) cumulative incidences was 2.5% at Month 24 and 2.4% at Month 36 (corresponding to the numbers needed to treat (NNTs) of 40 and 42 subjects). Robustness of the result for the key secondary CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure was corroborated by sensitivity analyses including a tipping point analysis (significance maintained with an inflation factor of 100%). The HR [95% CI] derived from the on-treatment analysis in the per-protocol population was 0.819 [0.686-0.978] (p=0.0272).

Subgroup analyses for the key secondary endpoint suggest some heterogeneity for the following factors: regions, age, renal function, and concomitant use of antihyperglycaemic agents known to improve CV outcomes in patients with T2DM (SGLT2 inhibitors and GLP-1 receptor agonists).

Other secondary endpoints were merely exploratory, but in line with the beneficial CV effect of finerenone described above. Specifically, finerenone numerically reduced all-cause mortality (HR [95% CI]: 0.895 [0.746-1.075]; ARR 0.9%) and all-cause hospitalisations (HR [95% CI]: 0.946 [0.876-1.022]; ARR 1.9%).

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6.4 Safety

Overall safety database – patient exposure

Exposure calculated for the safety analysis population (SAF) was balanced between the treatment arms over a median treatment duration of approximately 27 months.

	Finerenone N= 2827	Placebo N= 2831
Extent of exposure (overall, mg)		
n	2826 [a]	2831
Mean (SD)	12935.460 (7521.795)	14125.881 (7523.631)
Median	12200.000	13740.000
Min, Max	10.00,31090.00	20.00,30930.00
Mean daily dose (mg)		
n	2826	2831
Mean (SD)	15.138 (4.472)	16.480 (4.014)
Median	16.870	18.627
Min, Max	1.17,21.34	2.75,30.39

Summary of adverse events

The incidence of treatment-emergent adverse events (TEAEs) overall was similar between the treatment arms (89.8% versus 89.5%). Finerenone-treated patients had a higher incidence of TEAEs leading to permanent study treatment discontinuation (7.3 versus 5.9% for placebo), while the incidence of serious TEAEs leading to treatment discontinuation was balanced between treatment arms (2.7 versus 2.8%).

The overall incidence of serious TEAEs was numerically lower in the finerenone arm as compared with placebo (31.9% versus 34.3%). Likewise, fatal TEAEs (excluding outcome events) were less frequent in the finerenone arm (1.1% versus 1.8%).

TEAEs certainly more frequent in the finerenone arm as compared with placebo control were:

- Hyperkalaemia (446 [15.8%] vs 221 [7.8%])
- Glomerular filtration rate decreased (179 [6.3%] vs 133 [4.7%])
- Hypotension (126 [4.5%] vs 87 [3.1%])
- Pruritus (104 [3.7] vs 73 [2.6%])
- Blood potassium increased (81 [2.9%] vs 40 [1.4%])

In line with these findings, the higher overall incidence of study drug-related TEAEs in the finerenone arm (22.9% for finerenone versus 15.9% for placebo) was primarily driven by the MedDRA preferred terms «hyperkalaemia» and «blood potassium increased» (11.8 [finerenone] vs 4.8% [placebo]).

Serious AEs and Deaths

Serious TEAEs reported more frequently in the finerenone arm than in placebo control were acute kidney injury (2.0% vs 1.8%), hyperkalaemia (1.5% vs 0.4%), cellulitis (0.9% vs 0.8%), and cataract (0.7% vs 0.4%). Serious TEAEs assessed as related to study treatment were generally infrequent (1.7% and 1.2%), with hyperkalaemia (0.8% vs 0.2%) and acute kidney injury (0.3% vs 0.2%) representing the most common events.

The overall incidence of deaths was lower in the finerenone arm than in placebo control.

Adverse events of special interest

Hyperkalaemia

Hyperkalaemia regularly occurs in patients with advanced CKD and T2D aggravated by standard of care therapy with renin-angiotensin system (RAS) inhibitors (ACEI/ARB) as well as MRAs. The key findings from FIDELIO-DKD on treatment-emergent hyperkalaemia events were:

- There was a nearly 2-fold increase in the incidence of these events in the finerenone arm
- About ~2/3 of these events were considered to be related to study drug intake

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- The mean difference in serum potassium (finerenone – placebo) was approximately 0.2 mmol/L consistently across eGFR subgroups.
- The proportion of treatment-emergent hyperkalaemia events reported as serious (1.5% vs 0.4%), leading to permanent discontinuation of the study drug (2.3% vs 0.9%) or hospitalisation (1.4% vs 0.3%) was relatively small.
- No treatment-emergent hyperkalaemia events resulted in death; most events were mild or moderate at most.
- The majority of finerenone–treated patients recovered from treatment-emergent hyperkalaemia (~83.5% [13.2%/15.8%]) and increased blood potassium (~82.8% [2.4%/2.9%]).
- No unfavourable imbalance for the MedDRA system organ class (SOC) «Cardiac Disorders» was observed between treatment arms (11.1% vs 13.9%).
- No imbalance in other events related to severe clinical manifestations of hyperkalaemia, such as paraesthesia, peripheral neuropathy, or renal tubular acidosis was observed.

Worsening of renal function

As outlined above, the FIDELIO-DKD study demonstrated a long-term nephroprotective effect in the overall study population. Yet, finerenone-treated subjects exhibited an initial eGFR reduction (mean of 2 mL/min/1.73m^2) after starting treatment which diminished over time. The annualised chronic eGFR slope was less steep in the finerenone arm compared with placebo (between-group difference in the SAF: 1.31 mL/min/1.73m^2 per year). Moreover, hospitalisations or discontinuations of study drug due to worsening of renal function TEAEs were balanced between treatment arms.

Other TEAEs associated with mode of action of drug

Other TEAEs associated with the mode of action of an MRA and RAS blockade were hypotension and hyponatraemia. The incidence of the TEAE of hypotension was higher in the finerenone arm than in the placebo arm (4.5 vs 3.1%). Clinically relevant events typically associated with hypotension were less frequent in the finerenone arm (e.g., dizziness [5.2 versus 5.4%], syncope [1.2 versus 2.0%], or fall [1.6 versus 2.0%]).

The incidence of hyponatraemia was also higher for finerenone (1.3 vs 0.6%). These events were mainly non-serious, considered as unrelated to study drug, mild or moderate in intensity, and rarely led to treatment discontinuation.

AEs of gynaecomastia and breast pain typical for certain steroidal MRAs were rare in the FIDELIO-DKD trial with no meaningful imbalance between treatment arms: gynaecomastia 0.2% in both arms and breast pain 0.2% (finerenone) versus 0.1% (placebo).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Beneficial Effects and associated Uncertainties

Finerenone can be administered independently of food. For patients unable to swallow a tablet, it can be crushed and administered resuspended in water or applesauce.

The finerenone exposure increased proportionally to the administered dose across a range of 1.25 mg and 80 mg.

Finerenone did not accumulate after multiple dosing. There was no evidence of relevant time-dependent pharmacokinetics.

Mild, moderate or severe renal impairment, as well as mild or moderate hepatic impairment had no major effect on finerenone PK. The finerenone exposure was comparable in Asians and Caucasians after accounting for body weight. The finerenone PK was similar in healthy subjects, DN and DKD patients.

The interaction potential of finerenone as a perpetrator appeared to be low.

Finerenone caused no QTc prolongation at therapeutic and supratherapeutic exposures.

No data in subjects with severe hepatic impairment are available.

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Finerenone slowed progression of DKD in patients with T2DM.
The drug reduced the primary endpoint (composite of kidney failure, sustained decrease in eGFR ≥40%, or renal death) compared with placebo (HR [95% CI]: 0.825 [0.732 - 0.928]). The absolute risk reduction (ARR) for the primary endpoint amounted to 3.4% (504 subjects [17.8% | 7.59 events per 100 patient-years] versus 600 subjects [21.1% | 9.08 events per 100 patient-years]). A set of sensitivity analyses supported the robustness of this reduction in the primary endpoint. The beneficial effect on the composite primary endpoint was driven by a reduction of all its components apart from renal death (too few contributing events). The risk reduction became apparent ≥12 months following treatment onset and persisted thereafter. Results from secondary and exploratory renal endpoints were consistent with those for the primary endpoint.

Finerenone reduced major CV outcomes in patients with T2DM and DKD.
The drug significantly reduced the risk (HR [95 CI]: 0.860 [0.747-0.989]) of the key secondary endpoint (composite of CV death, non-fatal MI, non-fatal stroke, hospitalisation for HF [hHF]).
This beneficial effect was driven by all components of the secondary endpoint except for non-fatal strokes (HR [95 CI]: 1.027 [0.765-1.380]) and occurred early on after treatment onset. Exploratory secondary endpoints were also consistent with a CV benefit of finerenone. Finerenone-treated patients showed a numerical reduction in all-cause mortality (HR [95% CI]: 0.895 [0.746-1.075]) and all-cause hospitalisations (HR [95% CI]: 0.946 [0.876-1.022]).

There are findings for the primary endpoint suggesting heterogeneity of the treatment effect (e.g. depending on a prior history of CVD, baseline BMI, concomitant antihyperglycaemic treatment, and concurrent use of co-medications inhibiting/inducing CYP3A4). However, these are not reflected in the analyses for UACR, a major marker of the course of CKD.

Unfavourable Effects and associated Uncertainties
Despite the minimal impact of renal and hepatic impairment on finerenone exposure, dose adjustments in these patient populations are required due to potential hyperkalaemia**.**
Strong CYP3A4 inhibitors or inducers are expected to have a profound impact on finerenone exposure. Therefore, restrictions up to a contraindication of the co-administration of strong CYP3A4 inhibitors or inducers are required**.**
Finerenone increased the serum potassium levels, making dose adjustments based on serum potassium necessary**.**

The FIDELIO-DKD study (median treatment duration 27 months) revealed no prohibitive or unexpected safety concerns. Overall, there was no increase in the incidence of TEAEs / serious TEAEs in the finerenone arm versus placebo. TEAEs with fatal outcome were numerically less frequent in the finerenone arm, even disregarding the outcome events (OE). Fatal AEs and OEs occurred in 219 (7.7%) and 249 (8.8%) patients in the finerenone and placebo arms, respectively.

The increased overall incidence of study drug-related TEAEs (22.9% [finerenone] vs 15.9% [placebo]) was primarily driven by the MedDRA preferred terms «hyperkalaemia» and «blood potassium increased» (11.8 [finerenone] versus 4.8% [placebo]).

Serious TEAEs assessed as related to study treatment occurred in 1.7% [finerenone] and 1.2% [placebo] of the patients, where hyperkalaemia (0.8% versus 0.2%) and acute kidney injury (AKI) (0.3% versus 0.2%) again represented the most common events.

Only a rather small proportion of treatment-emergent hyperkalaemia events were serious (1.5% versus 0.4%), lead to permanent discontinuation of the study drug (2.3% versus 0.9%) or hospitalisation (1.4% versus 0.3%).

After starting treatment with finerenone, some decline in eGFR (difference [finerenone – placebo] in the FIDELIO-DKD trial: 2 mL/min/1.73 m^2) is expected. Accordingly, events of acute decreases in glomerular filtration rate were more frequent in the finerenone arm compared with placebo (6.3% versus 4.7%). Worsening of renal function TEAEs resulting in hospitalisation or discontinuation of study drug were similar between treatment arms. Vitally, the incidence of AKI was balanced between the treatment arms.

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Uncertainties regarding the Unfavourable Effects

Potential drug-drug interactions with finerenone represent an uncertainty with regard to safety, particularly in relation to hyperkalaemia. However, no unfavourable imbalances between treatment arms were detected for clinically relevant hyperkalaemia events. It is important to define the patient characteristics predisposing for hyperkalaemia clearly during finerenone treatment. A *post hoc* subgroup analysis suggested that patients with an eGFR ≥60 mL/min/1.73 m^2 at baseline were less vulnerable (smallest difference between treatment groups). Conversely, higher baseline serum potassium and a medical history of hyperkalaemia were associated with a higher rate of hyperkalaemia events.

Benefit-Risk Assessment

The overall clinical pharmacology profile of finerenone is favourable. The main issue is its interaction potential as a CYP3A4 substrate/victim of the respective CYP inhibitors and inducers, which is appropriately addressed in the information for healthcare professionals.

In patients with T2DM and CKD, finerenone reduces the risk of i) the progression of CKD and ii) major CV adverse events. Major risks related to finerenone treatment are hyperkalaemia and acute drop in glomerular filtration. The clinical benefit shown for finerenone outweighs these risks, which are appropriately addressed in the information for healthcare professionals.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Kerendia, film-coated tablets was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Kerendia®

Composition

Active substances

Finerenone.

Excipients

Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, hypromellose, sodium lauryl sulfate.
Film coating: Hypromellose, talc, titanium dioxide (E 171), ferric oxide red (E 172) (contained only in the 10 mg dose strength), ferric oxide yellow (E 172) (contained only in the 20 mg dose strength).
One 10 mg film-coated tablet contains 0.44 mg sodium and 42.75 mg lactose.
One 20 mg film-coated tablet contains 0.47 mg sodium and 38.00 mg lactose.

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 10 mg and 20 mg finerenone.

Appearance
10 mg: pink, oval 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.

20 mg: yellow, oval 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.

Indications/Uses

Kerendia is indicated to delay progression of chronic kidney disease in adult patients with type 2 diabetes mellitus (see sections “Dosage/Administration” and “Clinical efficacy”).
For study outcomes regarding the effects on cardiovascular events, see section “Clinical efficacy”.

Dosage/Administration

Usual dosage

The recommended target dose of Kerendia is 20 mg once daily (equivalent to the maximum daily dose).

Initiation of treatment

Kerendia should be used in addition to standard of care (see section “Clinical efficacy”).
Initiation of treatment with Kerendia is recommended when the serum potassium level is ≤ 4.8 mmol/L. For monitoring of serum potassium, see “Maintenance therapy”.
If the serum potassium level is > 4.8 to 5.0 mmol/L, initiation of treatment with Kerendia can be considered depending on patient characteristics and serum potassium level, with additional monitoring of serum potassium performed in the first 4 weeks (see section “Warnings and precautions”).
If the serum potassium level is > 5.0 mmol/L, treatment with Kerendia is not recommended (see section “Warnings and precautions”).
To determine the starting dose, the estimated glomerular filtration rate (eGFR) is measured. The starting dose of Kerendia is:

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

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

Maintenance therapy

Four weeks after initiation, re-start or up-titration of treatment with Kerendia, serum potassium and eGFR must be measured again. See Table 1 to determine continuation of treatment with Kerendia and dose adjustment. Thereafter, serum potassium should be measured periodically and measurement should be repeated as needed based on patient characteristics and serum potassium level (see sections “Warnings and precautions” and “Interactions”).

Table 1: Continuation (4 weeks after initiation, re-start or up-titration) of treatment with Kerendia and dose adjustment

Serum potassium (mmol/L)	**Kerendia dosage (from week 5)**
≤ 4.8	Maintain a dosage of 20 mg once daily. For patients on a dosage of 10 mg once daily, increase the dosage to 20 mg once daily if eGFR has not decreased by > 30% compared to the previous measurement.
> 4.8-5.5	Maintain dosage.
> 5.5	Withhold Kerendia. Restart at 10 mg once daily when serum potassium is ≤ 5.0 mmol/L.

Special dosage instructions

Patients with hepatic disorders

In patients with severe hepatic impairment (Child-Pugh C), treatment with Kerendia must be avoided (see sections “Warnings and precautions” and “Pharmacokinetics”).
In patients with mild to moderate hepatic impairment, no initial dose adjustment is required (Child-Pugh A or B) (see section “Pharmacokinetics”).
In patients with moderate hepatic impairment (Child-Pugh B), additional monitoring of serum potassium should be considered and monitoring should be adapted according to patient characteristics (see sections “Warnings and precautions” and “Pharmacokinetics”).

Patients with renal disorders

Initiation of treatment

In patients with eGFR ≥ 25 to < 60 mL/min/1.73 m^2, the starting dose of Kerendia is 10 mg once daily.
In patients with eGFR < 25 mL/min/1.73 m^2, initiation of treatment with Kerendia is not recommended due to limited clinical experience (see sections “Warnings and precautions” and “Pharmacokinetics”).

Maintenance therapy

In patients with mild, moderate or severe renal impairment, continued treatment with Kerendia and dose adjustment should proceed based on serum potassium.
To determine whether the starting dose can be increased to the recommended daily dose, the eGFR should be determined 4 weeks after initiation of treatment. See Table 1 and “Maintenance therapy”.
In patients with end-stage renal failure (eGFR < 15 mL/min/1.73 m^2), treatment with Kerendia should be continued cautiously with regard to the serum potassium level, as clinical experience is limited (see section “Warnings and precautions”).

Combination therapy

In all patients already being treated with a moderate CYP3A4 inhibitor, therapy with Kerendia should be initiated at a starting dose of 10 mg once daily (see sections “Warnings and precautions” and “Interactions”).

Body weight

No dose adjustment based on body weight is required (see section “Pharmacokinetics”).

Elderly patients

No dose adjustment based on age is required (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Kerendia in patients under 18 years have not been investigated.

Delayed administration

A missed dose should be taken as soon as possible, but only on the same day. No double dose should be taken on the same day to make up for a missed dose.

Mode of administration

For oral use.
The tablets can be taken with a glass of water independently of meals (see section "Pharmacokinetics").
Taking Kerendia together with grapefruit or grapefruit juice must be avoided (see sections "Warnings and precautions" and "Interactions").
For patients unable to swallow whole tablets, the tablets can be crushed immediately prior to use and taken with water or semi-solid foods (such as apple puree) (see section "Pharmacokinetics").

Contraindications

Kerendia is contraindicated in patients:

- receiving concomitant treatment with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) (see section "Interactions").
- who have Addison's disease.
- who are hypersensitive to the active substance or to any of the excipients (see sections "Composition" and "Warnings and precautions").

Warnings and precautions

Hyperkalaemia

Hyperkalaemia has been observed in patients treated with Kerendia (see section "Undesirable effects").
Some patients are at increased risk of developing hyperkalaemia. Risk factors include reduced eGFR, increased serum potassium and previous episodes of hyperkalaemia. More frequent monitoring should be considered in these patients.
Initiation of treatment with Kerendia is not recommended if the serum potassium level is > 5.0 mmol/L. If the serum potassium level is > 4.8 to 5.0 mmol/L, initiation of treatment with Kerendia can be considered depending on patient characteristics and serum potassium level, with additional monitoring of serum potassium performed in the first 4 weeks (see section "Dosage/Administration").
Administration of Kerendia in treated patients should be suspended if the serum potassium level is > 5.5 mmol/L. Local guidelines for the treatment of hyperkalaemia must be observed. Treatment with Kerendia is re-started at a dosage of 10 mg once daily when serum potassium is ≤ 5.0 mmol/L (see section "Dosage/Administration").

In all patients, serum potassium and eGFR must be measured again four weeks after initiation, re-start or up-titration of treatment with Kerendia. Thereafter, serum potassium should be measured periodically and measurement should be repeated as needed based on patient characteristics and serum potassium level (see section “Dosage/Administration”).

Concomitant treatment

The risk of hyperkalaemia can also increase in patients taking concomitant medications that can increase the serum potassium level (see section “Interactions”). See also “Concomitant use of substances that affect finerenone exposure”.
Concomitant use of Kerendia with the following medicinal products must be avoided:

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

Kerendia must be used with caution and the serum potassium level must be monitored when Kerendia is taken concomitantly with the following medicinal products:

- potassium supplements
- trimethoprim or trimethoprim-sulfamethoxazole. Temporary discontinuation of treatment with Kerendia may be required.

Renal impairment

The risk of hyperkalaemia increases with decreasing renal function. Continuous monitoring of renal function should be performed as needed in accordance with standard practice (see section “Dosage/Administration”).
Initiation of treatment with Kerendia is not recommended in patients with eGFR < 25 mL/min/1.73 m^2 due to limited clinical experience (see sections “Dosage/Administration” and “Pharmacokinetics”).
In patients with end-stage renal failure (eGFR < 15 mL/min/1.73 m^2), treatment with Kerendia should be continued cautiously with regard to the serum potassium level, as clinical experience is limited (see section “Dosage/Administration”).

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section “Pharmacokinetics”). Due to an expected substantial increase in finerenone exposure, the use of Kerendia in patients with severe hepatic impairment should be avoided (see section “Dosage/Administration”).
Due to an increase in finerenone exposure, additional monitoring of serum potassium should be considered in patients with moderate hepatic impairment (Child-Pugh B) and monitoring should be adapted according to patient characteristics (see sections “Dosage/Administration” and “Pharmacokinetics”).

Concomitant use of substances that affect finerenone exposure

Moderate and weak CYP3A4 inhibitors

When Kerendia is co-administered with moderate CYP3A4 inhibitors (e.g. erythromycin and verapamil) or weak CYP3A4 inhibitors (e.g. amiodarone and fluvoxamine), increased finerenone exposure is expected (see section “Interactions”). The serum potassium level must therefore be monitored, particularly during initiation of treatment with - or when changing the dosage of - Kerendia or the CYP3A4 inhibitor (see section “Dosage/Administration”).

Strong and moderate CYP3A4 inducers

Concomitant use of Kerendia with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s wort) or moderate CYP3A4 inducers (e.g. efavirenz) that markedly decrease the plasma concentrations of finerenone and lead to a reduced therapeutic effect must be avoided (see section “Interactions”). Use of an alternative co-medication with no or weak potential to induce CYP3A4 should be considered.

Grapefruit

Concomitant ingestion of grapefruit or grapefruit juice must be avoided, as this increases the plasma concentration of finerenone (see sections “Dosage/Administration” and “Interactions”).

Information on excipients

Kerendia contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Kerendia contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet; that is to say essentially “sodium-free”.

Interactions

Interaction studies have been performed in adults only. Finerenone is eliminated almost exclusively via cytochrome P450 (CYP)-mediated oxidative metabolism (mainly via CYP3A4 [90%] and, to a minor extent, via CYP2C8 [10%]).

Effect of other medicinal products on Kerendia

Enzyme inhibitors

Strong CYP3A4 inhibitors

Concomitant use of Kerendia with itraconazole, clarithromycin and other strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, nelfinavir (not approved in Switzerland), cobicistat, telithromycin (not

approved in Switzerland) or nefazodone (not approved in Switzerland) is contraindicated, as a significant increase in finerenone exposure can be expected (see section “Contraindications”). Simulations show that concomitant use of Kerendia with itraconazole (200 mg twice daily) increases finerenone exposure (geometric mean ratio (GMR) and 90% population interval for AUC and C_{max}: 6.31 [3.36-11.41] and 2.37 [1.76-3.31]). Clarithromycin (500 mg twice daily) also leads to an anticipated increase in finerenone exposure (GMR and 90% population interval for AUC and C_{max}: 5.28 [2.88-10.48] and 2.25 [1.76-2.98]).

Moderate CYP3A4 inhibitors

Concomitant use of erythromycin (500 mg thrice daily), a moderate CYP3A4 inhibitor, increased mean finerenone exposure (GMR and 90% confidence interval for AUC and C_{max}: 3.48 [3.02-4.02] and 1.88 [1.63-2.17]). Another moderate CYP3A4 inhibitor, verapamil (240 mg controlled-release tablet once daily), increased mean finerenone exposition (GMR and 90% confidence interval for AUC and C_{max}: 2.70 [2.43-3.01] and 2.22 [1.88-2.62]). Since serum potassium can rise as a result, the serum potassium level must be monitored (see sections “Dosage/Administration” and “Warnings and precautions”).

Weak CYP3A4 inhibitors

Simulations indicate that fluvoxamine (100 mg twice daily), a weak CYP3A4 inhibitor, increases finerenone exposure (GMR and 90% population interval for AUC and C_{max}: 1.57 [1.25-2.08] and 1.38 [1.18-1.64]). Since serum potassium can rise as a result, the serum potassium level must be monitored (see sections “Dosage/Administration” and section “Warnings and precautions”).

Grapefruit

Concomitant intake of grapefruit or grapefruit juice is likely to increase the plasma concentration of finerenone and should be avoided (see sections “Dosage/Administration” and “Warnings and precautions”).

Enzyme inducers

Concomitant use of Kerendia with rifampicin and other strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, St John’s wort), or with efavirenz and other moderate CYP3A4 inducers is not recommended. These CYP3A4 inducers markedly reduce the plasma concentrations of finerenone and lead to reduced therapeutic effect (see section “Warnings and precautions”). Simulations indicate that rifampicin (600 mg once daily), a strong CYP3A4 inducer, reduces finerenone exposure (GMR and 90% population interval for AUC and C_{max}: 0.07 [0.05-0.11] and 0.14

[0.11-0.21]). Efavirenz (600 mg once daily), a moderate CYP3A4 inducer, reduces finerenone exposure (GMR and 90% population interval for AUC and C_{max}: 0.19 [0.14-0.27] and 0.32 [0.23-0.43]).

Pharmacodynamic interactions

Medicinal products that increase serum potassium

Medicinal products that increase serum potassium can be expected to increase the risk of hyperkalaemia when used concomitantly with Kerendia.
Concomitant use of Kerendia with the following medicinal products should be avoided:

- potassium-sparing diuretics (e.g. amiloride, triamterene (not approved in Switzerland))
- other mineralocorticoid receptor antagonists (MRAs) (e.g. eplerenone, spironolactone, esaxerenone (not approved in Switzerland) canrenone (not approved in Switzerland))

Kerendia should be used with caution when co-administered with the following medicinal products and the serum potassium level must be monitored during treatment:

- potassium supplements
- trimethoprim or trimethoprim-sulfamethoxazole. Temporary discontinuation of treatment with Kerendia may be required (see section “Warnings and precautions”).

Effect of Kerendia on other medicinal products

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

Pregnancy, lactation

Women of childbearing potential

Women who can become pregnant should use effective contraception during treatment with Kerendia.

Pregnancy

There are no data on the use of Kerendia in pregnant women. Animal studies have shown embryofoetal developmental toxicity after exposure in excess to the maximum human exposure (see section “Preclinical data”).
Kerendia should not be used during pregnancy, unless treatment with finerenone is required due to the woman’s clinical condition.

Lactation

It is unknown whether finerenone or its metabolites are excreted in human milk. Available pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk (see section “Preclinical data”). A risk for breast-fed newborns and infants cannot be excluded. A decision must be made as to whether breastfeeding should be interrupted or whether treatment with Kerendia should be avoided, taking into account both the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of Kerendia on human fertility. Animal studies with finerenone revealed no clinically relevant indications of any risk of impaired fertility (see section “Preclinical data”).

Effects on ability to drive and use machines

Based on the safety profile of Kerendia, no influence on the ability to drive and use machines is anticipated.

Undesirable effects

Summary of the safety profile

The safety of Kerendia in patients with chronic kidney disease and type 2 diabetes was evaluated in the pivotal phase III study FIDELIO-DKD. In this study, 2827 patients received Kerendia (10 mg or 20 mg once daily) and 2831 patients received a placebo. For patients in the Kerendia group, the mean duration of treatment was 2.2 years.

The most commonly reported (≥ 10%) adverse drug reaction with Kerendia was hyperkalaemia (see “Description of selected adverse reactions” below and section “Warnings and precautions”).

List of adverse drug reactions

The adverse drug reactions observed with Kerendia are summarised in Table 2 below according to MedDRA system organ classes and frequency categories. Adverse drug reactions are listed by system organ class and in order of decreasing frequency, using the following convention: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

Table 2: Adverse drug reactions

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

[1] includes Blood potassium increased and Hyperkalaemia
[2] includes Blood sodium decreased and Hyponatraemia
[3] includes Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension
[4] In patients treated with Kerendia, the mean systolic blood pressure (SBP) decreased by 3 mmHg and the mean diastolic blood pressure (DBP) decreased by 1-2 mmHg at month 1 and remained stable thereafter. The majority of hypotension events were mild or moderate and resolved spontaneously. Events associated with hypotension, such as dizziness, syncope or fall, occurred no more frequently in patients on Kerendia than with placebo.
[5] An initial decrease in eGFR (mean 2 mL/min/1.73 m^2) attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation (see section “Properties/Effects”).

Description of selected adverse drug reactions

Hyperkalaemia

In the FIDELIO-DKD study, hyperkalaemia events were reported in 18.3% of patients treated with Kerendia, compared with 9.0% of placebo-treated patients. In patients treated with Kerendia, the majority of hyperkalaemia events were mild to moderate. The proportion of hospitalisations for hyperkalaemia was 1.4% for the finerenone group versus 0.3% in the placebo group. The frequency of hyperkalaemia leading to permanent discontinuation of the study product was 2.3% in patients on finerenone versus 0.9% in the placebo group.
An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the Kerendia arm compared to placebo, with a maximum between-group difference of 0.23 mmol/L observed after 4 months and remaining stable thereafter (see section “Properties/Effects”). For specific recommendations, see sections “Dosage/Administration” and “Warnings and precautions”.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of adverse events associated with Kerendia overdose in humans have been reported. The most likely sign of an overdose is anticipated to be hyperkalaemia. If hyperkalaemia develops,

standard treatment according to local guidelines should be initiated. Treatment with Kerendia should be continued according to Table 1 (see section “Dosage/Administration”).
Finerenone is unlikely to be efficiently removed by haemodialysis, as the fraction bound to plasma proteins is about 90%.

Properties/Effects

ATC code

C03DA05

Mechanism of action

Finerenone is a non-steroidal, selective antagonist of the mineralocorticoid receptor (MR) and effectively attenuates inflammation and fibrosis mediated by MR overactivation. The MR is expressed in the kidneys, heart and blood vessels, where finerenone also counteracts sodium retention and hypertrophic processes. Finerenone has a high potency and selectivity for the MR due to its non-steroidal structure and bulky binding mode. Finerenone has no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors and therefore causes no sex hormone-related adverse reactions (such as gynaecomastia). 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.

Pharmacodynamics

Effects in healthy subjects

Finerenone (multiple doses of 10 mg and 20 mg twice daily or 40 mg once daily over 10 days) had no consistent effect on natriuresis or urine potassium in healthy male subjects. These regimens led to activation of the renin-angiotensin-aldosterone system (RAAS), i.e. reversible increases in plasma renin activity and serum aldosterone concentrations, with baseline values reached again within 48 hours after the last dose.
However, following MR activation with the MR agonist fludrocortisone (0.5 mg), finerenone (single doses of 2.5, 5, 10, 20 mg PEG solution or 20 mg tablets) showed dose-dependent natriuretic effects in healthy male subjects. Moreover, finerenone (at doses of 5 to 20 mg) significantly decreased urinary potassium excretion compared to placebo.
Single or multiple doses of finerenone had no influence on vital signs in healthy subjects.

Effects on patients with chronic kidney disease and type 2 diabetes

In FIDELIO-DKD, a randomised, double-blind, placebo-controlled, multicentre Phase III study in adults with chronic kidney disease and type 2 diabetes, the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio (UACR) in patients randomised to treatment with finerenone was 31% after 4 months and UACR remained at a reduced level throughout the entire study.

Cardiac electrophysiology

A thorough QT study in 57 healthy subjects produced no indications of a QT/QTc-prolonging effect for finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic), suggesting that finerenone has no effect on cardiac repolarisation.

Clinical efficacy

The FIDELIO-DKD study was a randomised, double-blind, placebo-controlled, multicentre Phase III study investigating the effect of finerenone compared to placebo on renal and cardiovascular outcomes in adult patients with type 2 diabetes and chronic kidney disease (inclusion criteria: a) moderately increased albuminuria [UACR ≥ 30 - < 300 mg/g] and eGFR 25 - 60 mL/min/1.73 m^2 with concomitant presence of diabetic retinopathy OR b) severely increased albuminuria [UACR ≥ 300 mg/g] and eGFR 25 - 75 mL/min/1.73 m^2). Patients enrolled onto the study were required to have a serum potassium level of ≤ 4.8 mmol/L and to have received previous treatment with standard of care, including a maximum tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi [34%]) or an angiotensin receptor blocker (ARB [66%]). Patients with chronic NYHA Class II-IV heart failure were excluded from the study.

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

The study investigated 5674 patients randomly assigned at a 1:1 ratio to treatment with finerenone once daily (n = 2833) or placebo (n = 2841). The starting dose was either 10 mg [for an eGFR of 25 – < 60 mL/min/1.73 m^2] or 20 mg [for an eGFR of ≥ 60 mL/min/1.73 m^2]). The dose strength was adjusted during the course of the study to 10 mg or 20 mg QD, mainly based on the serum potassium level. Median follow-up was 2.6 years. The trial population was 63% white, 25% Asian and 5% black. Mean age at recruitment was 66 years and 70% of patients were male. Mean baseline eGFR was 44.3 mL/min/1.73 m^2 and 55% of patients had an eGFR of < 45 mL/min/1.73 m^2. Median UACR was 852 mg/g; mean glycated haemoglobin A1c (HbA_{1c}) was 7.7%. About 46% of study participants had a previous atherosclerotic cardiovascular disease, 30% had a history of coronary artery disease and 8% had a history of cardiac failure. Mean blood pressure was 138/76 mmHg. The mean duration from diagnosis of type 2 diabetes at study inclusion was 16.6 years and, at study baseline, almost all study participants (97%) were in receipt of one or more antidiabetic agents (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). In addition, 47% and 26% of patients had pre-existing diabetic retinopathy and

diabetic neuropathy, respectively, at study baseline. The majority of patients were also receiving a statin (74%) and/or a calcium channel blocker (63%).

The FIDELIO-DKD study demonstrated superiority of treatment with finerenone versus placebo for the combined (renal) primary endpoint (HR 0.82, 95% CI 0.73–0.93, p = 0.0014; see Table 3 and Figure 1).

Furthermore, finerenone significantly reduced the risk for the combined (cardiovascular) key secondary endpoint (HR 0.86, 95% CI 0.75–0.99, p = 0.0339; see Table 3 and Figure 2). In the finerenone arm, lower incidence rates were seen compared to the placebo arm with regard to heart failure, non-fatal myocardial infarction and cardiovascular death. Non-fatal stroke occurred at a similar incidence in both treatment arms (see Table 3).

Table 3: Analysis of the primary and main secondary time-to-event endpoints (and their individual components) in the Phase III study FIDELIO-DKD

	Patients with chronic kidney disease and type 2 diabetes					
	Finerenone* 10 or 20 mg once daily n = 2833		**Placebo* n = 2841**		**Treatment effect Finerenone/Placebo**	
Primary and secondary time-to-event endpoints:	**n (%)**	**Event rate (100 pt.y.)**	**n (%)**	**Event rate (100 pt.y.)**	**Hazard ratio (95% CI)**	**p-value**
Primary combined endpoint “kidney failure, sustained ≥ 40 % decrease in eGFR or renal death”	504 (17.8%)	7.59	600 (21.1%)	9.08	0.82 [0.73; 0.93]	0.0014
Kidney failure	208 (7.3%)	2.99	235 (8.3%)	3:39	0.87 [0.72; 1:05]	-
Sustained ≥ 40 % decrease in eGFR	479 (16.9%)	7:21	577 (20.3%)	8.73	0.81 [0.72; 0.92]	-
Renal death	2 (< 0.1%)	-	2 (< 0.1%)	-	-	-
Secondary combined endpoint “CV death, non-fatal MI, non-fatal stroke or hospitalisation for heart failure”	367 (13.0%)	5:11	420 (14.8%)	5.92	0.86 [0.75; 0.99]	0.0339
CV death	128 (4.5%)	1.69	150 (5.3%)	1.99	0.86 [0.68; 1:08]	-
Non-fatal MI	70 (2.5%)	0.94	87 (3.1%)	1.17	0.80 [0.58; 1:09]	-
Non-fatal stroke	90 (3.2%)	1.21	87 (3.1%)	1.18	1:03 [0.76; 1:38]	-
Hospitalisation for heart failure	139 (4.9%)	1.89	162 (5.7%)	2.21	0.86 [0.68; 1:08]	-

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

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

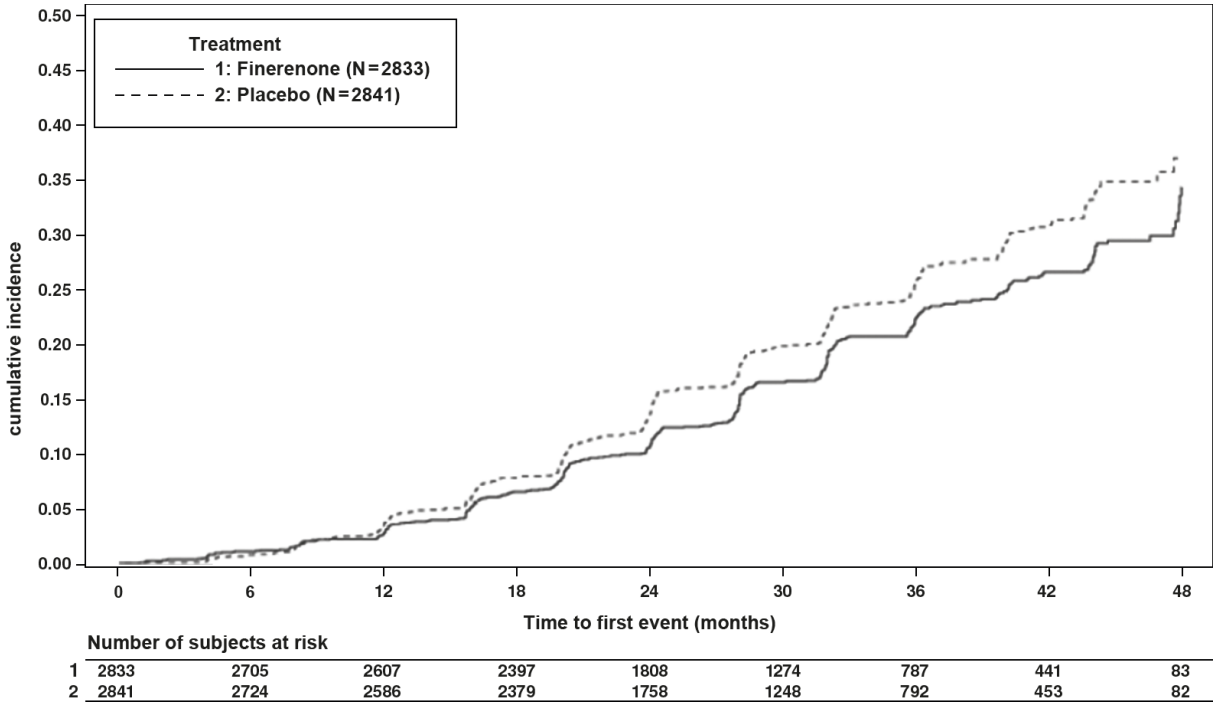
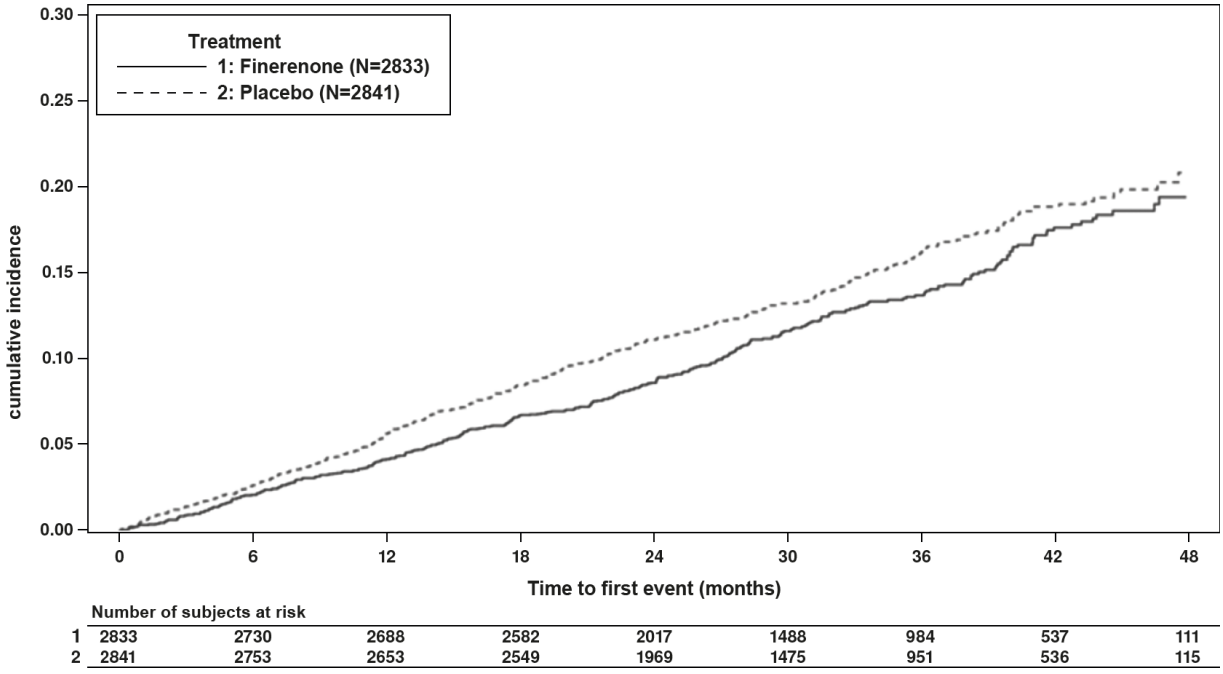


Figure 2: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for heart failure in the FIDELIO-DKD study



Pharmacokinetics

Absorption

Finerenone is almost completely absorbed after oral administration. Absorption is rapid, with peak plasma concentrations (C_{max}) reached 0.5 to 1.25 hours after tablet ingestion in the fasted state. The absolute bioavailability of finerenone is 43.5% due to first-pass metabolism in the intestinal wall and liver. Finerenone is not a substrate of the efflux transporter P-gp *in vivo*.
Intake with high-fat, high-calorie food increased the AUC of finerenone by 21%, reduced C_{max} by 19% and prolonged the time to reach C_{max} to 2.5 hours. This is not clinically relevant. Therefore, finerenone can be taken independently of meals (see section “Dosage/Administration”).

Distribution

For finerenone, the steady state (V_{ss}) volume of distribution is 52.6 L. Human plasma protein binding of finerenone *in vitro* is 91.7%, with serum albumin being the main binding protein.

Metabolism

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. Four major metabolites (M-1a, M-1b, M-2a and M-3a) were found in plasma. All metabolites are pharmacologically inactive.

Elimination

Finerenone elimination from plasma is rapid, with an elimination half-life ($t_{1/2}$) of about 2 to 3 hours. Excretion of unchanged finerenone represents a minor excretory pathway (< 1% of dose in the urine via glomerular filtration, < 0.2% in the faeces). About 80% of the administered dose was excreted via urine and around 20% of the dose via faeces, almost exclusively in the form of metabolites. With a systemic clearance of about 25 L/h, finerenone can be classified as an active substance with low clearance.

Linearity/non-linearity

Finerenone pharmacokinetics are linear across the investigated dose range from 1.25 to 80 mg.

Kinetics in specific patient groups

Hepatic impairment

In cirrhotic patients with mild hepatic impairment (Child-Pugh A), no change in finerenone exposure was shown.
In cirrhotic patients with moderate hepatic impairment (Child-Pugh B), the mean AUC of finerenone was increased by 38% and C_{max} was unchanged compared to healthy control subjects (see section “Dosage/Administration”).

There are no data for patients with severe hepatic impairment (Child-Pugh C) (see sections “Dosage/Administration” and “Warnings and precautions”).

Renal impairment

Mild renal impairment (creatinine clearance [CL_{CR}] 60 to < 90 mL/min) had no influence on the AUC and C_{max} of finerenone. Compared to subjects with normal renal function (CL_{CR} ≥ 90 mL/min), the effect of moderate (CL_{CR} 30 to < 60 mL/min) or severe (CL_{CR}< 30 mL/min) renal impairment on the AUC of finerenone was similarly high, with increases of 34-36%. Moderate or severe renal impairment had no effects on C_{max} (see section “Dosage/Administration”).
Due to the high plasma protein binding, finerenone is not expected to be dialysable.

Elderly patients

58% of the 2827 patients who received finerenone in the FIDELIO-DKD study were 65 years old or older and 15% were 75 years old or older. Overall, no differences in safety or efficacy were observed between these patients and younger patients.
Elderly patients (≥ 65 years) exhibited higher plasma concentrations of finerenone than younger patients (≤ 45 years), with mean AUC and C_{max} values being 34% and 51% higher in the elderly (see section "Dosage/Administration”).

Body weight

In population pharmacokinetic analyses, body weight was shown to be a covariate for V_c/F, leading to higher finerenone C_{max} values in subjects with a lower body weight. The C_{max} of a person with a body weight of 50 kg was estimated to be 43% to 51% higher than in a person of 100 kg. Dose adjustment based on body weight is not required (see section “Dosage/Administration”).

Preclinical data

Non-clinical data reveal no special hazard for humans at clinically relevant concentrations, based on conventional studies of safety pharmacology, acute toxicity and phototoxicity.
Effects observed in repeat-dose toxicity studies were mainly due to exaggerated pharmacodynamic activities of finerenone and secondary adaptive responses.

Reproductive toxicity

In rats, male fertility was not influenced by doses of up to 30 mg/kg/day finerenone (16 times the $AUC_{unbound}$ in humans). Finerenone caused reduced fertility in female rats (reduced number of corpora lutea and implantation sites), as well as signs of early embryonic toxicity (increased post-implantation losses and reduced number of viable foetuses) at about 21 times the $AUC_{unbound}$ in humans. In addition, reduced ovarian weight was found at about 17 times the human $AUC_{unbound}$. At 10 times the human $AUC_{unbound}$, no effects on female fertility and early embryonic development were observed.

In the embryofoetal toxicity studies in rats, oral administration of finerenone led to reduced placental weight and signs of embryofoetal toxicity, including reduced foetal weight and delayed ossification at the maternally toxic dose of 10 mg/kg/day and more. This was equivalent to an $AUC_{unbound}$ 19 times above clinical exposure. 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). The $AUC_{unbound}$ is about 25 times above clinical exposure. The NOAEL of 3 mg/kg/day (low dose) in rats revealed a safety margin equivalent to 10 times the $AUC_{unbound}$. In rabbits, the NOAEL of 2.5 mg/kg/day (high dose) revealed a safety margin equivalent to 13 times the $AUC_{unbound}$.
In the pre- and postnatal development study in rats, increased pup mortality and other adverse findings (lower pup weight, delayed pinna unfolding) were observed at a dose of 3 mg/kg/day or more. In addition, the pups in this dose group showed slightly increased locomotor activity, but no other neurobehavioural changes starting from an $AUC_{unbound}$ roughly 4 times above clinical exposure. The NOAEL of 1 mg/kg/day revealed a safety margin roughly equivalent to twice the $AUC_{unbound}$. The increased locomotor activity in the offspring might indicate a potential risk for the foetus.

Genotoxicity

Finerenone did not induce mutations in the microbial mutagenesis assay (Ames test). *In vitro*, finerenone induced no chromosomal aberrations in Chinese hamster V79 lung cells. In the micronucleus test in male mice *in vivo*, intraperitoneal finerenone at concentrations of up to 1000 mg/kg/day were not clastogenic. Overall, finerenone showed no genotoxic potential.

Carcinogenicity

In 2-year carcinogenicity studies, oral administration of finerenone did not show any carcinogenic potential in male and female rats or in female mice. In male mice, finerenone led to an increase in Leydig cell adenomas at a dose of 30 mg/kg/day, which is equivalent to an $AUC_{unbound}$ 26 times above clinical exposure. A dose of 10 mg/kg/day, which is equivalent to an $AUC_{unbound}$ 17 times above clinical exposure, caused no tumors. Based on the known sensitivity of rodents to develop these tumors, as well as the pharmacology-based mechanism at supratherapeutic doses and the adequate safety margins, the increase in Leydig cell tumors in male mice is not rated as clinically relevant.

Other information

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Special precautions for storage

Keep out of the reach of children.
Do not store above 30°C.

Store in the original packaging.

Authorisation number

68130 (Swissmedic).

Packs

10 mg film-coated tablets: Packs of 28 or 98 film-coated tablets and hospital packs of 1 × 100 film-coated tablets (B)
20 mg film-coated tablets: Packs of 28 or 98 film-coated tablets and hospital packs of 1 × 100 film-coated tablets (B)

Marketing authorisation holder

Bayer (Schweiz) AG, Zurich

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