Summary Report of Benefit-Risk Assessment

KERENDIA FILM-COATED TABLET 10MG AND 20MG

NEW DRUG APPLICATION

Active Ingredient(s)	Finerenone
Product Registrant	Bayer (South East Asia) Pte Ltd
Product Registration Number	SIN16387P, SIN16388P
Application Route	Full evaluation
Date of Approval	25 November 2021

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A INTRODUCTION

Kerendia, in addition to standard of care, is indicated to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and hospitalisation for heart failure in adults with chronic kidney disease and albuminuria associated with type 2 diabetes.

The active substance, finerenone, is an oral, non-steroidal selective antagonist of the mineralocorticoid receptor (MR) that attenuates inflammation and fibrosis mediated by MR overactivation.

Kerendia is available as film-coated tablets containing 10 mg and 20 mg of finerenone. Other ingredients in the tablet core are microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate and sodium laurilsulfate. Ingredients in the film coating include ferric oxide red (only for Kerendia 10 mg film-coated tablet), ferric oxide yellow (only for Kerendia 20 mg film-coated tablet), hypromellose, talc and titanium dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, finerenone, is manufactured at [redacted]. The drug products, Kerendia Film-coated Tablet 10 mg and 20 mg, are manufactured at Bayer AG, Leverkusen, Germany.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data were adequate to support the approved storage condition and re-test period. [redacted]. The drug substance is approved for storage at 25°C with a re-test period of 24 months.

Drug product:
[redacted]. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when store at or below 30°C. The container closure system is PVC/PVDC-Aluminium blisters.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of finerenone was based on data from one pivotal study, FIDELIO-DKD (Study 16244).

The FIDELIO-DKD study was a Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven study that compared finerenone with placebo in adult patients with type 2 diabetes and chronic kidney disease (CKD) who either had urine albumin-to-creatinine ratio (UACR) of 30 to <300 mg/g, an eGFR of 25 to <60 mL/min/1.73 m^2 and presence of diabetic retinopathy, or UACR ≥300 mg/g and an eGFR of 25 to <75 mL/min/1.73 m^2. All patients were to have a serum potassium ≤4.8 mmol/L at screening. The study excluded patients with known significant non-diabetic kidney disease.

Patients were randomised in a 1:1 ratio to receive either oral finerenone or placebo once daily in addition to their standard of care therapy that included a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB). The starting dose of finerenone was based on the patient's eGFR at the screening visit: 10 mg once daily in patients with an eGFR of 25 to <60 mL/min/1.73 m^2, and 20 mg once daily in patients with an eGFR of ≥60 mL/min/1.73 m^2. The dose of finerenone could be titrated during the study, with a target dose of 20 mg daily if the serum potassium was ≤4.8 mmol/L and the eGFR decrease was less than 30% below the value measured at the last scheduled visit. Down-titration of the finerenone dose was only performed for safety reasons.

The primary efficacy endpoint was the time to first occurrence of the renal composite of sustained decline in eGFR of ≥40% from baseline over at least 4 weeks, onset of kidney failure (defined as chronic dialysis, kidney transplantation, or sustained decrease in eGFR to <15 mL/min/1.73m^2 over at least 4 weeks), or renal death. The key secondary endpoint was the time to first occurrence of the composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalisation for heart failure. Other secondary endpoints include time to all-cause mortality, time to all-cause hospitalisation, change in UACR from baseline to Month 4 and the time to first occurrence of the composite of the onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death. The weighted Bonferroni-Holm procedure was used for the primary and key secondary endpoints, followed by hierarchical testing of the remaining secondary efficacy endpoints.

A total of 5,734 patients were randomised into the study and 5,674 were analysed in the Full Analysis Set, comprising 2,833 patients in the finerenone arm and 2,841 patients in the placebo arm. The median treatment duration was 27.04 months (range: 0.00 to 51.48 months) in the

finerenone arm and 27.20 months (range: 0.00 to 51.52 months) in the placebo arm. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 66.0 years (range: 28.0 to 97.0 years), and 895 (15.8%) patients were ≥75 years of age. The majority of patients were male (70.2%), White (63.3%) or Asian (25.4%). The mean (SD) eGFR value at baseline was 44.34 (12.56) mL/min/1.73 m^2, 87.5% of patients had very high albuminuria (UACR ≥ 300 mg/g) and the median UACR at baseline was 851.87 mg/g. At baseline, 45.9% of the patients had a history of CV disease and the mean duration of diabetes was 16.56 ± 8.77 years. The most frequently used non-antidiabetic treatments at baseline were ARBs (65.7%), ACEIs (34.2%) and statins (74.3%).

Treatment with finerenone statistically significantly reduced the risk of the primary renal composite endpoint by 17.5% compared to placebo (hazard ratio [HR] 0.825; 95% CI 0.732, 0.928; p=0.0014). The reductions in the individual components of sustained decline in eGFR of ≥40% from baseline and kidney failure were consistent with that for the composite renal endpoint (HR of 0.815 and 0.869, respectively). There were too few renal deaths (2 events in each arm) to reach a conclusion on the treatment effect of finerenone on renal death.

Finerenone also demonstrated a statistically significant risk reduction in the key secondary composite CV endpoint by 14% compared to placebo (HR 0.860; 95% CI 0.747; 0.989; p=0.0339). The individual components of CV death, non-fatal MI and hospitalisation for heart failure showed a consistent relative risk reduction as that for the composite CV endpoint (HR of 0.855, 0.796 and 0.857, respectively). There was no benefit of finerenone over placebo for the non-fatal stroke component as the incidence rates were similar between the treatment arms (3.2% in the finerenone arm vs. 3.1% in the placebo arm) (HR 1.027; 95% CI 0.765, 1.380).

The other secondary endpoints were tested hierarchically, starting with all-cause mortality. In the study, a total of 219 patients (7.7%) in finerenone arm and 244 patients (8.6%) in placebo arm had died, but the difference did not reach statistical significance (HR 0.895; 95% CI 0.746, 1.075; p=0.2348). Hence, the difference between finerenone and placebo was not formally tested for the remaining endpoints. For all-cause hospitalisation, the comparison of finerenone with placebo showed a HR of 0.946 (95% CI 0.876, 1.022), with 1,263 patients (44.6%) in finerenone arm and 1,321 patients (46.5%) in placebo arm being hospitalised due to any cause.

The reduction in UACR from baseline to Month 4 was larger in the finerenone arm than the placebo arm by 31.2% (LS-mean ratio 0.688; 95% CI 0.662, 0.715). The secondary renal endpoint composite of kidney failure, sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death, occurred in 8.9% of patients in finerenone arm and 11.5% of patients in placebo arm (HR 0.763; 95% CI: 0.648, 0.900). These results further supported the findings of the primary composite renal endpoint.

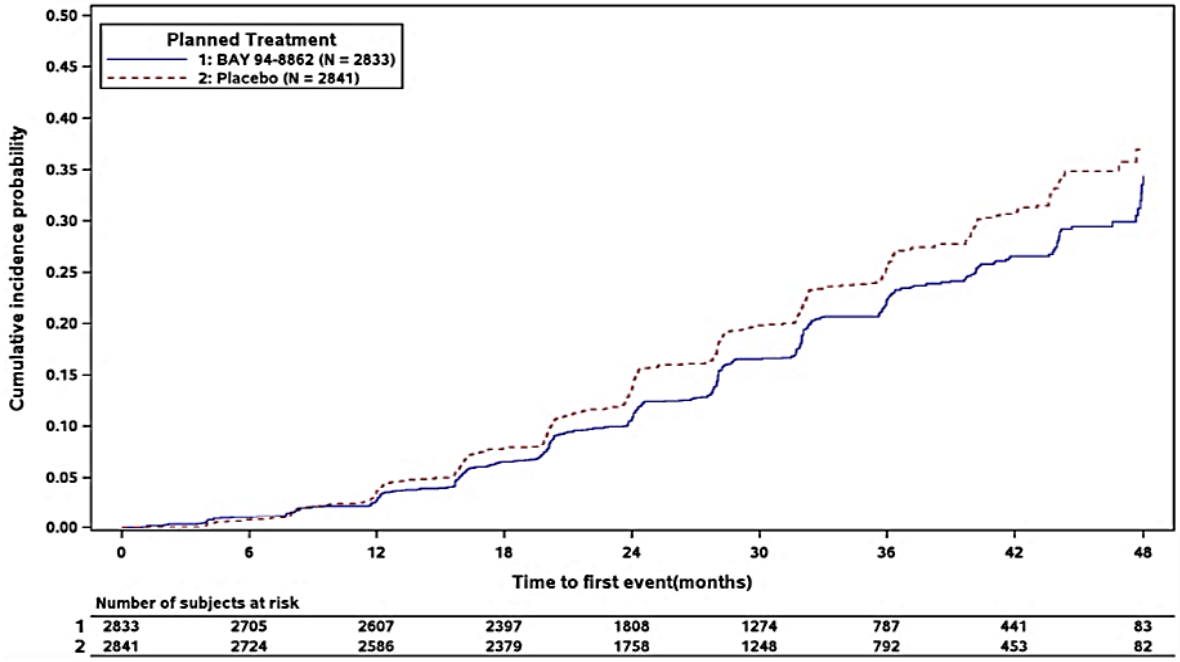
Summary of Key Efficacy Endpoints (Study FIDELIO-DKD)*

	Finerenone (N = 2833)	Placebo (N = 2841)	Hazard ratio (95% CI)	p-value
Primary endpoint				
Composite of kidney failure, sustained decrease of eGFR ≥40% from baseline, or renal death, n (%)	504 (17.8%)	600 (21.1%)	0.825 (0.732, 0.928)	0.0014
Sustained decrease in eGFR ≥40%	479 (16.9%)	577 (20.3%)	0.815 (0.722, 0.920)	0.0009
Kidney failure	208 (7.3%)	235 (8.3%)	0.869 (0.721, 1.048)	0.1409
End-stage kidney disease	119 (4.2%)	139 (4.9%)	0.858 (0.672, 1.096)	0.2191

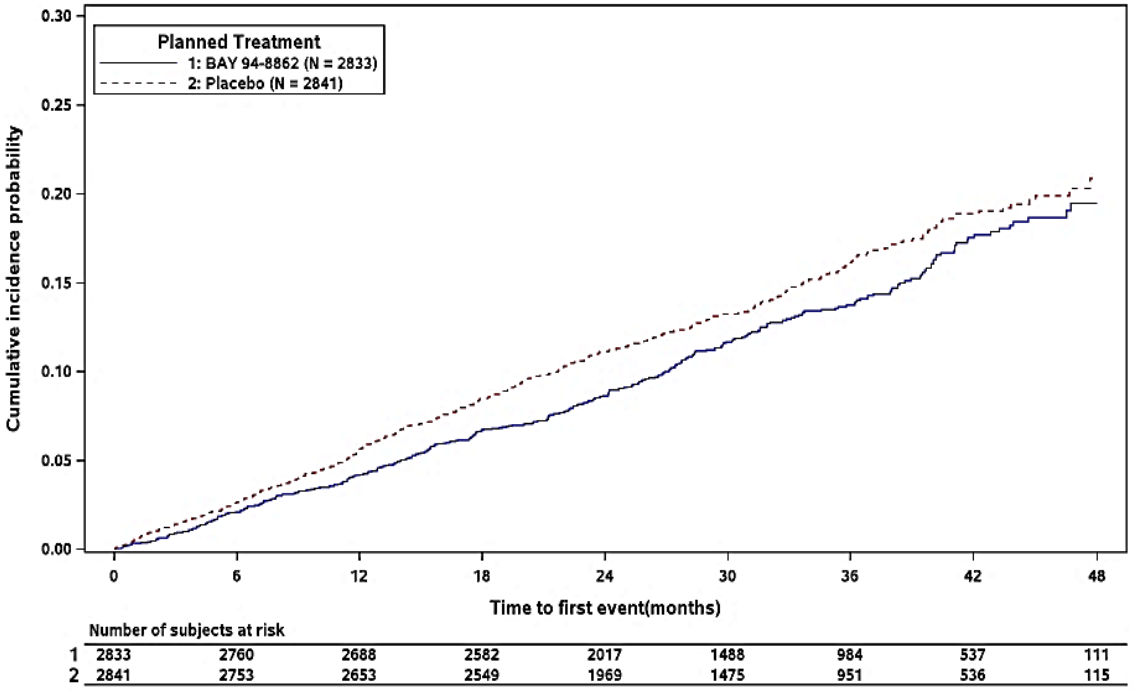
Sustained decrease in eGFR to <15 mL/min	167 (5.9%)	199 (7.0%)	0.824 (0.671, 1.013)	0.0646
Renal death	2 (<0.1%)	2 (<0.1%)	-	-
Key secondary endpoint				
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure, n (%)	367 (13.0%)	420 (14.8%)	0.860 (0.747, 0.989)	0.0339
CV death	128 (4.5%)	150 (5.3%)	0.855 (0.675, 1.083)	0.1927
Non-fatal MI	70 (2.5%)	87 (3.1%)	0.796 (0.581, 1.090)	0.1540
Non-fatal stroke	90 (3.2%)	87 (3.1%)	1.027 (0.765, 1.380)	0.8579
Hospitalization for heart failure	139 (4.9%)	162 (5.7%)	0.857 (0.683, 1.076)	0.1821
Other secondary endpoints				
All-cause mortality, n (%) CV death Renal death Fatal, non-CV/non-renal	219 (7.7%) 128 (4.5%) 2 (<0.1%) 89 (3.1%)	244 (8.6%) 150 (5.3%) 2 (<0.1%) 92 (3.2%)	0.895 (0.746, 1.075) 0.855 (0.675, 1.083) - 0.958 (0.716, 1.283)	0.2348 0.1927 - 0.7751
All-cause hospitalisation, n (%) CV hospitalisation Hospitalisation due to heart failure	1263 (44.6%) 519 (18.3%) 139 (4.9%)	1321 (46.5%) 561 (19.7%) 162 (5.7%)	0.946 (0.876, 1.022) 0.918 (0.815, 1.035) 0.857 (0.683, 1.076)	0.1623 0.1617 0.1821
Change in UACR from baseline to Month 4 (mg/g)**	0.6550	0.9524	0.688 (0.662, 0.715)	<0.0001
Composite of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death, n (%)	252 (8.9%)	326 (11.5%)	0.763 (0.648, 0.900)	0.0012
Sustained decrease in eGFR ≥57%	167 (5.9%)	245 (8.6%)	0.675 (0.555, 0.822)	<0.0001

*presented in the sequence of hierarchical testing
**For this continuous endpoint, geometric means are displayed in the place of incidences as descriptive values and the ratio of Least-Squares means and F-test p-value from an ANCOVA are displayed in place of the Hazard Ratio and log rank test p-value as inferential statistics.
eGFR: estimated glomerular filtration rate; CV: cardiovascular; MI: myocardial infarction; UACR: uurinary albumin-to-creatinine ratio

Kaplan-Meier curves for time to first occurrence of primary renal composite endpoint (Study FIDELIO-DKD)



Kaplan-Meier curves for time to first occurrence of secondary CV composite endpoint (Study FIDELIO-DKD)



Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary and secondary endpoints across subgroups analysed, including region (North America, Europe, Asia, Latin America, rest of the world), baseline eGFR (<25 mL/min/1.73m^2, 25 - <45 mL/min/1.73m^2, 45 - <60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2), baseline albuminuria (UACR < 30 mg/g, UACR 30 - <300 mg/g, UACR ≥300 mg/g), history of CV disease (present, absent), baseline BMI (<30 kg/m^2, ≥30 kg/m^2), gender (male, female), age at run-in visit (<65 years, ≥65 years), baseline serum potassium (≤4.4 mmol/L, >4.4 mmol/L), baseline haemoglobin A1C (≤7.5%, >7.5%), SGLT-2 inhibitors at baseline (yes, no), GLP-1 agonists at baseline (yes, no), and baseline waist circumference (normal, increased, substantially increased), demonstrating robustness of data.

Overall, the results in study FIDELIO-DKD adequately supported the efficacy of finerenone in reducing the risk of sustained eGFR decline, end-stage kidney disease, CV death, non-fatal myocardial infarction, and hospitalisation for heart failure in adult patients with CKD and albuminuria associated with type 2 diabetes.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of finerenone in patients with CKD and albuminuria associated with type 2 diabetes were mainly derived from Study FIDELIO-DKD, comprising a total of 5,658 patients (2,827 patients in the finerenone arm and 2,831 patients in the placebo arm). The total exposure of patients to study drug was similar in the treatment arms - 6,346 patient-years in finerenone arm and 6,431 patient-years in placebo arm. The median study duration for patients in the Safety Analysis Set was 31.74 months in the finerenone arm and 31.74 months in the placebo arm.

Overall of Safety Profile (Study FIDELIO-DKD, Safety Analysis Set)

Number (%) of patients with:	Finerenone (N = 2827)	Placebo (N = 2831)
Any AE [a]	2540 (89.8%)	2535 (89.5%)
Any AE related to procedures required by protocol	63 (2.2%)	66 (2.3%)
Any AE leading to discontinuation of study drug	233 (8.2%)	188 (6.6%)
Any serious AE	1113 (39.4%)	1148 (40.6%)
Any AE with outcome death [c]	89 (3.1%)	105 (3.7%)
Any TEAE	2468 (87.3%)	2478 (87.5%)
Any study drug-related TEAE	646 (22.9%)	449 (15.9%)
Any TEAE related to procedures required by protocol	52 (1.8%)	54 (1.9%)
Any TEAE leading to discontinuation of study drug	207 (7.3%)	168 (5.9%)
Any serious TEAE	902 (31.9%)	971 (34.3%)
Any study drug-related serious TEAE	48 (1.7%)	34 (1.2%)
Any serious TEAE related to procedures required by protocol	2 (<0.1%)	4 (0.1%)
Any serious TEAE leading to discontinuation of study drug	75 (2.7%)	78 (2.8%)
Any TEAE with outcome death [c]	31 (1.1%)	51 (1.8%)
Any post-treatment [b] AEs	919 (32.5%)	851 (30.1%)
Any AE related to procedures required by protocol	5 (0.2%)	5 (0.2%)
Any serious AE	404 (14.3%)	415 (14.7%)
Any AE with outcome death [c]	58 (2.1%)	54 (1.9%)

[a] The category contains any AEs that were reported during the trial, including those that potentially occurred between randomisation and first study drug intake for patients who did not take their first dose at the date of randomisation
[b] These refer to patients with events recorded more than 3 days after stop of study drug intake
[c] Excluding outcome events
AE: adverse event, N: number of patients, TEAE: treatment-emergent AE

The proportion of patients with treatment-emergent adverse events (TEAEs) was similar across treatment arms (87.3% in the finerenone arm vs 87.5% in the placebo arm). TEAEs that were reported more frequently in the finerenone arm compared to the placebo arm included hyperkalaemia (15.8% vs 7.8%), decreased GFR (6.3% vs 4.7%) and anaemia (7.4% vs 6.7%). The majority of the TEAEs were mild or moderate in severity. TEAEs related to study drug were reported at a higher incidence in finerenone arm (22.9%) compared to the placebo arm (15.9%) and was driven by higher number of patients with study drug-related hyperkalaemia (10.1% in the finerenone arm vs 4.0% in the placebo arm).

TEAEs leading to the permanent discontinuation of the study drug were reported more frequently in the finerenone arm than the placebo arm (7.3% vs 5.9%). The difference was driven by the higher number of patients who permanently discontinued the study drug due to hyperkalaemia events.

The adverse event of special interest reported for finerenone was hyperkalaemia, which is a known AE of mineralocorticoid receptor antagonists. There was no evidence of an increased incidence of any severe clinical cardiac manifestations of hyperkalaemia (e.g. bradycardia, ventricular arrhythmia or sudden cardiac death) in the study. Hyperkalaemia is manageable with dose interruptions and/or dose modifications and this has been described in the package insert.

Overall, the safety profile of finerenone 10 mg or 20 mg once daily in patients with CKD and albuminuria associated with type 2 diabetes is similar to other mineralocorticoid receptor antagonists, with hyperkalaemia being the predominant adverse event, and the finerenone-related AEs were manageable through dosing interruption and/or dose reduction.

E ASSESSMENT OF BENEFIT-RISK PROFILE

CKD and type 2 diabetes are major global health concerns. An estimated 20% to 40% of patients with type 2 diabetes develop CKD, and individuals with type 2 diabetes and microalbuminuria have an increased risk of premature CV disease. Alongside dietary and lifestyle interventions, current pharmacological strategies for management of CKD associated with type 2 diabetes include optimisation of therapies for the control of glycaemia, blood pressure and blood lipid levels, as well as ACEIs and ARBs. Despite current therapies, there remains a substantial risk of progression of kidney disease and CV events in the target patient population.

The FIDELIO-DKD study demonstrated that finerenone in addition to standard of care therapy statistically significantly reduced the composite risk of renal events (kidney failure, sustained decrease of eGFR ≥40% or renal death) by 17.5% compared to placebo (HR 0.825; 95% CI 0.732; 0.928; p=0.0014). The reduction in UACR from baseline to Month 4 was 31.2% greater in finerenone arm compared to placebo arm, and the composite of kidney failure, sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death risk was reduced by 23.7% with finerenone compared to placebo. In addition, finerenone also statistically significantly reduced the composite risk of CV events (CV death, non-fatal MI and hospitalisation for heart failure) compared to placebo by 14% (HR 0.860; 95% CI 0.747; 0.989; p=0.0339). There was no benefit of finerenone over placebo for non-fatal stroke event.

The safety profile of finerenone was similar to other mineralocorticoid receptor antagonists. Finerenone 10 mg or 20 mg once daily was well tolerated as finerenone-related AEs were manageable through dosing interruption and/or dose reduction. Hyperkalaemia is an adverse event of special interest for finerenone, and it has been adequately addressed in the local package insert via the provision of relevant warnings and precautions as well as dose adjustment recommendations.

Overall, the benefit-risk profile of finerenone in addition to standard of care for adult patients with CKD and albuminuria associated with type 2 diabetes was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of Kerendia in addition to standard of care to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalisation for heart failure in adults with CKD and albuminuria associated with type 2 diabetes outweighed the risks. Approval of the product registration was granted on 25 November 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

Kerendia 10 mg film-coated tablets
Kerendia 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kerendia 10 mg film-coated tablet
Each film-coated tablet contains 10 mg finerenone.

Kerendia 20 mg film-coated tablet
Each film-coated tablet contains 20 mg finerenone.

3. PHARMACEUTICAL FORM

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

Kerendia 20 mg film-coated tablet
Pale-yellow, oval-oblong tablet with a length of 10 mm and a width of 5 mm, marked ´20´ on one side and ´FI´ on the other side

4. CLINICAL PARTICULARS

4.1 Indication(s)

Kerendia, in addition to standard of care, is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure in adults with chronic kidney disease and albuminuria associated with type 2 diabetes.

4.2 Dosage and method of administration

4.2.1 Method of administration
Oral use
Tablets may be taken with a glass of water and with or without food *(see section 'Pharmacokinetic properties')*.

Avoid taking Kerendia with grapefruit or grapefruit juice *(see section ´*Special warnings and precautions for use*´and '*4.5 Interaction with other medicinal products and other forms of interaction*')*.

For patients who are unable to swallow whole tablets, Kerendia tablet may be crushed and mixed with water or soft foods, such as applesauce, immediately prior to use and administered orally *(see section 'Pharmacokinetic properties')*.

4.2.2 Dosage regimen
The recommended target dose of Kerendia is 20 mg once daily.

4.2.2.1 Initiation of treatment
Initiation of Kerendia treatment is recommended when serum potassium ≤ 4.8 mmol/L.
For monitoring of serum potassium, see 'Continuation of treatment.'
If serum potassium > 4.8 to 5.0 mmol/L, initiation of Kerendia treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels *(see section ´*Special warnings and precautions for use*´)*.

If serum potassium > 5.0 mmol/L, initiation of Kerendia treatment is not recommended *(see section ´*Special warnings and precautions for use*´).*

Measure estimated glomerular filtration rate (eGFR) to determine the starting dose.
The starting dose of Kerendia is:
- 20 mg once daily if eGFR ≥ 60 mL/min/1.73 m^2
- 10 mg once daily if eGFR ≥ 25 to < 60 mL/min/1.73 m^2

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

4.2.2.2 Continuation of treatment
Four weeks after initiation or re-start or up-titration of Kerendia treatment, remeasure serum potassium and eGFR. See Table 1 to determine continuation of Kerendia treatment and dose adjustment.

Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels *(see section '*Special warnings and precautions for use*' and '*4.5 Interaction with other medicinal products and other forms of interaction*').*

Table 1: Continuation of Kerendia treatment and dose adjustment

Serum potassium (mmol/L)	**Kerendia dose (after 4 weeks and thereafter)**
≤ 4.8	Maintain 20 mg once daily. For patients on 10 mg once daily, increase the dose to 20 mg once daily if eGFR has not decreased > 30% compared to the prior measurement.
> 4.8 – 5.5	Maintain dose.
> 5.5	Withhold Kerendia. Restart at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.

4.2.2.3 Missed doses
A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the dose should be skipped, and the next dose taken as prescribed. Two doses should not be taken to make up for a missed dose.

The maximum daily dose of Kerendia is 20 mg.

4.2.3 Additional information on special populations
4.2.3.1 Patients with renal impairment
Initiation of Kerendia treatment
In patients with eGFR ≥ 25 to < 60 mL/min/1.73 m^2, the starting dose of Kerendia is 10 mg once daily. See section 'Initiation of treatment.'

In patients with eGFR < 25 mL/min/1.73m^2, initiation of Kerendia treatment is not recommended as clinical experience is limited *(see section '*Special warnings and precautions for use*' and section 'Pharmacokinetic properties').*

Continuation of Kerendia treatment
In patients with mild, moderate or severe renal impairment, continue Kerendia treatment and adjust dose based on serum potassium. Measure eGFR 4 weeks after initiation to determine up-titration. See Table 1 and section 'Continuation of treatment.'
In patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2), continue Kerendia treatment with caution regarding serum potassium levels as clinical experience is limited *(see section '*Special warnings and precautions for use*').*

4.2.3.2 Patients with hepatic impairment

In patients with severe hepatic impairment (Child Pugh C), avoid treatment with Kerendia *(see section 'Special warnings and precautions for use' and section 'Pharmacokinetic properties')*. In patients with mild or moderate hepatic impairment, no initial dose adjustment is required (Child Pugh A or B) *(see section 'Pharmacokinetic properties')*.

In patients with moderate hepatic impairment (Child Pugh B), consider additional serum potassium monitoring and adapt monitoring according to patient characteristics *(see section 'Special warnings and precautions for use' and section 'Pharmacokinetic properties')*.

4.2.3.3 Patients taking concomitant medications

In patients taking Kerendia concomitantly with moderate or weak CYP3A4 inhibitors, potassium supplements, trimethoprim, or trimethoprim-sulfamethoxazole, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics and make Kerendia treatment decisions as directed in Table 1. Temporary discontinuation of Kerendia when taking trimethoprim, or trimethoprim-sulfamethoxazole, may be necessary *(see sections 'Special warnings and precautions for use' and 'Interaction with other medicinal products and other forms of interaction')*.

4.2.3.4 Pediatric patients

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

4.2.3.5 Geriatric patients

No dose adjustment is required in the elderly *(see section 'Pharmacokinetic properties')*.

4.2.3.6 Gender

No dose adjustment is required based on gender *(see section 'Pharmacokinetic properties')*.

4.2.3.7 Body weight

No dose adjustment is required based on body weight *(see section 'Pharmacokinetic properties')*.

4.2.3.8 Ethnic differences

No dose adjustment is required based on ethnic differences *(see section 'Pharmacokinetic properties')*.

4.2.3.9 Smoking status

No dose adjustment is required based on smoking status *(see section 'Pharmacokinetic properties')*.

4.3 Contraindications

Kerendia is contraindicated in patients:

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

4.4 Special warnings and precautions for use

4.4.1 Hyperkalemia

Hyperkalemia has been observed in patients treated with Kerendia.
Some patients are at a higher risk to develop hyperkalemia. Risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalemia. Consider more frequent monitoring in these patients.

Initiation of Kerendia treatment is not recommended if serum potassium > 5.0 mmol/L. If serum potassium > 4.8 to 5.0 mmol/L, initiation of Kerendia treatment may be considered with additional

serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels *(see section* 'Dosage and method of administration').
Withhold Kerendia in treated patients if serum potassium > 5.5 mmol/L. Follow local guidelines for the management of hyperkalemia. Restart Kerendia at 10 mg once daily if serum potassium ≤ 5.0 mmol/L *(see section* 'Dosage and method of administration').

Remeasure serum potassium and eGFR in all patients 4 weeks after initiation or re-start or up-titration of Kerendia treatment. Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels *(see section* 'Dosage and method of administration').

Concomitant medications
The risk of hyperkalemia also may increase with the intake of concomitant medications that may increase serum potassium *(see section ´*Interaction with other medicinal products and other forms of interaction*´)*. See also 'Concomitant use of substances that affect finerenone exposure.'

Avoid concomitant use of Kerendia with the following medications:
- potassium-sparing diuretics (e.g., amiloride, triamterene)
- other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, esaxerenone, spironolactone, canrenone)

Use Kerendia with caution and monitor serum potassium when taken concomitantly with the following medications:
- potassium supplements
- trimethoprim, or trimethoprim-sulfamethoxazole. Temporary discontinuation of Kerendia may be necessary.

4.4.2 Renal impairment

The risk of hyperkalemia increases with decreasing renal function. Ongoing monitoring of renal function should be performed as needed according to standard practice *(see section* 'Dosage and method of administration' *and section ´Pharmacokinetic properties')*.
Initiation of Kerendia treatment is not recommended in patients with eGFR < 25 mL/min/1.73 m^2 as clinical experience is limited *(see section* 'Dosage and method of administration'*)*.
Continue Kerendia treatment with caution regarding serum potassium levels in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) as clinical experience is limited *(see section* 'Dosage and method of administration'*)*.

4.4.3 Hepatic impairment

Patients with severe hepatic impairment (Child Pugh C) have not been studied *(see section ´Pharmacokinetic properties'*). Due to an expected significant increase in finerenone exposure, avoid use of Kerendia in patients with severe hepatic impairment *(see section* 'Dosage and method of administration').
Due to an increase in finerenone exposure, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics in patients with moderate hepatic impairment (Child Pugh B) *(see section* 'Dosage and method of administration' and *section ´Pharmacokinetic properties'*)*.)*.

4.4.4 Concomitant use of substances that affect finerenone exposure

Moderate and weak CYP3A4 inhibitors
The concomitant use of Kerendia with moderate CYP3A4 inhibitors (e.g., erythromycin and verapamil) and weak CYP3A4 inhibitors (e.g., amiodarone and fluvoxamine) is expected to increase finerenone exposure *(see section '*Interaction with other medicinal products and other forms of interaction*')*. Monitor serum potassium especially during initiation of or changes to dosing of Kerendia or the CYP3A4 inhibitor *(see section* 'Dosage and method of administration'*)*.

Strong and moderate CYP3A4 inducers

Avoid concomitant use of Kerendia with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) or moderate CYP3A4 inducers (e.g., efavirenz), which are expected to markedly decrease finerenone plasma concentrations and result in reduced therapeutic effect (see section 'Interaction with other medicinal products and other forms of interaction'). Consider selection of an alternate concomitant medicinal product with no or weak potential to induce CYP3A4.

Grapefruit
Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone *(see sections* 'Dosage and method of administration' *and* 'Interaction with other medicinal products and other forms of interaction*').*

4.4.5 Embryo-fetal toxicity
Animal data have shown reproductive toxicity *(see section 'Preclinical safety data')*. The relevance for humans is unknown . Kerendia should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus. If the patient becomes pregnant while taking Kerendia, the patient should be informed of potential risks to the fetus. Advise women of childbearing potential to use effective contraception during treatment with Kerendia. Advise women not to breastfeed during treatment with Kerendia *(see section* 'Fertility, pregnancy and lactation'*).*

4.5 Interaction with other medicinal products and other forms of interaction

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

4.5.1.1 Effect of CYP3A4 inhibitors on finerenone
Strong CYP3A4 inhibitors
Simulations suggest that concomitant use of Kerendia with itraconazole (200 mg BID), a strong CYP3A4 inhibitor, increases finerenone AUC (+531%) and C_{max} (+137%). Clarithromycin (500 mg BID), another strong inhibitor, also is predicted to increase finerenone AUC (+428%) and C_{max} (+125%). Due to an expected marked increase in finerenone exposure, concomitant use of Kerendia with itraconazole, clarithromycin and other strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, nelfinavir, cobicistat, telithromycin or nefazodone) is contraindicated (*see section* 'Contraindications').

Moderate CYP3A4 inhibitors
Concomitant use of erythromycin (500 mg thrice daily), a moderate CYP3A4 inhibitor, increased finerenone mean AUC and Cmax by 248% and 88%, respectively. Another moderate CYP3A4 inhibitor, verapamil (240 mg controlled-release tablet once daily), increased finerenone mean AUC and Cmax by 170% and 122%, respectively. Serum potassium may increase, and therefore, monitoring of serum potassium is recommended *(see sections* 'Dosage and method of administration' *and* 'Special warnings and precautions for use*')*.

Weak CYP3A4 inhibitors
In an analysis of Kerendia in patients, the use of amiodarone, a weak CYP3A4 inhibitor, was estimated to result in a 21% increase of finerenone AUC. Simulations suggest that fluvoxamine (100 mg BID), another weak inhibitor, increases finerenone AUC (+57%) and C_{max} (+38%). Serum potassium may increase, and therefore, monitoring of serum potassium is recommended *(see sections* 'Dosage and method of administration' *and* ' Special warnings and precautions for use*')*.

Grapefruit
Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentration of finerenone and should be avoided *(see sections* 'Dosage and method of administration' *and* 'Special warnings and precautions for use*')*.

4.5.1.2 Effect of strong and moderate CYP3A4 inducers on finerenone

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

4.5.1.3 Lack of clinically relevant drug-drug interaction

Concomitant use of gemfibrozil (600 mg twice-daily), a strong inhibitor of CYP2C8, increased finerenone mean AUC and C_{max} by 10% and 16%, respectively. This is not clinically relevant.
Pre- and co-treatment with the proton pump inhibitor omeprazole (40 mg once daily) had no effect on finerenone mean AUC and mean C_{max}.
Concomitant use of antacid aluminum hydroxide and magnesium hydroxide (70 mVal) had no effect on finerenone mean AUC and reduced its mean C_{max} by 19%. This is not clinically relevant.

4.5.2 Effect of finerenone on other substances

In vivo a multiple-dose regimen of 20 mg finerenone once-daily had no effect on the AUC of the CYP3A4 probe substrate midazolam. Finerenone neither inhibits nor induces CYP3A4.
A single dose of 20 mg finerenone also had no effect on AUC and Cmax of the CYP2C8 probe substrate repaglinide. Finerenone does not inhibit CYP2C8.
Lack of mutual pharmacokinetic interaction was demonstrated between finerenone and the CYP2C9 substrate warfarin. Finerenone had no effect on AUC and C_{trough} of the P-gp substrate digoxin at steady-state (90% CI of ratio (digoxin + finerenone / digoxin alone) within 90-111%). The ratio of digoxin C_{max} at steady-state (digoxin + finerenone / digoxin alone) was 105.3% with a 90% CI of 94.65-117.16 %.

4.5.3 Pharmacodynamic interactions

<u>Medications that increase serum potassium</u>
It is anticipated that medications that increase serum potassium will increase the risk of hyperkalemia when used concomitantly with Kerendia.
Concomitant use of Kerendia with the following medications should be avoided:

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

Kerendia should be used with caution and serum potassium monitored when taken concomitantly with the following medications:

- potassium supplements
- trimethoprim, or trimethoprim - sulfamethoxazole. Temporary discontinuation of Kerendia may be necessary.

(See section 'Special warnings and precautions for use')

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

There are no data on the use of Kerendia in pregnant women . Animal studies have shown embryo-fetal developmental toxicity at exposures in excess to the maximum human exposure. In the pre- and post-natal developmental toxicity study, slightly increased locomotor activity was found in the offspring, which may have been caused by exposure during pregnancy *(see section 'Preclinical safety data')*.
Kerendia should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus *(see section ´Special warnings and precautions for use´).*

4.6.2 Lactation
It is unknown whether finerenone or its metabolites are excreted in human breast milk. Available pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk. Rat pups exposed by this route showed adverse effects. A risk to the nursing infant cannot be excluded. Breastfeeding should be discontinued if use of Kerendia is considered essential *(see section ´*Special warnings and precautions for use*´).*

4.6.3 Fertility
No human data on the effect of Kerendia on fertility is available. Animal studies with finerenone did not indicate a risk of impaired male fertility. Animal studies with finerenone indicated impaired female fertility at exposures considered sufficiently in excess to the maximum human exposure indicating no clinical relevance *(see section 'Preclinical safety data').*

4.6.4 Women of childbearing potential / Contraception
Kerendia may cause embryo-fetal harm when administered during pregnancy. Women of childbearing potential should use effective contraception during treatment with Kerendia *(see section ´*Special warnings and precautions for use*´).*

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable effects

4.8.1 Summary of the safety profile
The safety of Kerendia in patients with chronic kidney disease associated with type 2 diabetes was evaluated in the pivotal phase III study FIDELIO-DKD. In this study, 2,827 patients received Kerendia (10 or 20 mg once daily) and 2,831 received placebo. For patients in the Kerendia group, the mean duration of treatment was 2.2 years.
The most frequently reported (≥ 10%) adverse reaction was hyperkalemia. See 'Description of selected adverse reactions' below *(see section '*Special warnings and precautions for use*').*

4.8.2 Tabulated list of adverse reactions
The adverse reactions reported with Kerendia are summarized in Table 2 below by MedDRA system organ class and by frequency.
Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using the following convention:
very common (≥1/10)
common (≥1/100 to <1/10)
uncommon (≥1/1,000 to <1/100)
rare (≥1/10,000 to <1/1,000)
very rare (<1/10,000)

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

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

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

[1] includes Blood potassium increased and Hyperkalemia
[2] includes Blood sodium decreased and Hyponatremia

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

4.8.3 Description of selected adverse reactions

Hyperkalemia

In the FIDELIO-DKD study, hyperkalemia events were reported in 18.3% of Kerendia-treated patients compared with 9.0% of placebo-treated patients. In patients treated with Kerendia, the majority of hyperkalemia events were mild to moderate. An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the Kerendia arm compared to placebo, with a maximum between-group difference of 0.23 mmol/L observed at Month 4, remaining stable thereafter. For specific recommendations, refer to sections ‘Dosage and method of administration’ and ‘Special warnings and precautions for use.’

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: aldosterone antagonists

ATC Code: C03DA05

5.1.1 Mechanism of action

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

fibrotic mediators.

5.1.2 Pharmacodynamic properties

5.1.2.1 Cardiac electrophysiology

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

5.1.3 Clinical efficacy and safety

5.1.3.1 Chronic kidney disease associated with type 2 diabetes

The FIDELIO-DKD study was a randomized, double-blind, placebo-controlled, multicenter Phase III study investigating the effect of Kerendia compared to placebo on kidney and cardiovascular outcomes in adult patients with chronic kidney disease associated with type 2 diabetes. Patients were eligible based on evidence of persistent albuminuria (≥30 mg/g to <300 mg/g) and eGFR ≥25 but <60 mL/min/1.73 m^2 and presence of diabetic retinopathy or persistent albuminuria (≥300 mg/g to 5,000 mg/g) and eGFR ≥25 to <75 mL/min/1.73 m^2, serum potassium ≤ 4.8 mmol/L at screening, and were required to be receiving standard of care, including a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with known significant non-diabetic kidney disease. Patients with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) were excluded.

The primary endpoint in the FIDELIO-DKD study was a composite of time to first occurrence of kidney failure (defined as chronic dialysis or kidney transplantation, or a sustained decrease in eGFR to < 15 ml/min/1.73 m^2 over at least 4 weeks), a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death. The key secondary endpoint was a composite of time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for heart failure.

The trial analyzed 5,674 patients randomly assigned to receive either Kerendia 10 mg or 20 mg once daily (N=2833), or placebo (N=2841), with a median follow-up duration of 2.6 years. After the end of study notification, vital status was obtained for 99.7% of patients. The trial population was 63% White, 25% Asian and 5% Black. The mean age at enrollment was 66 years and 70% of patients were male. At baseline, the mean eGFR was 44.3 ml/min/1.73 m^2, with 55% of patients having an eGFR < 45 ml/min/1.73 m^2, median urine albumin-to-creatinine ratio (UACR) was 852 mg/g, and mean glycated hemoglobin A1c (HbA1c) was 7.7%, 46% had a history of atherosclerotic cardiovascular disease, 30% had history of coronary artery disease, 8% had a history of cardiac failure, and the mean blood pressure was 138/76 mmHg. The mean duration of type 2 diabetes at baseline was 16.6 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 47% and 26% of patients at baseline, respectively. At baseline, almost all patients were on ACEi (34%) or ARB (66%), and 97% of patients used one or more antidiabetic medications (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). The other most frequent medications taken at baseline were statins (74%) and calcium channel blockers (63%).

Kerendia demonstrated superiority to placebo by significantly reducing the risk of the primary composite endpoint compared to placebo in a time-to-event analysis using the Cox proportional hazards model and log-rank test (HR 0.82, 95% CI 0.73-0.93, p=0.0014). See Figure 1/Table 3 below. Kerendia also significantly reduced the risk of the key secondary composite endpoint of time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure compared to placebo (HR 0.86, 95% CI 0.75-0.99, p=0.0339). See Figure 2. Prespecified secondary time-to-event endpoints are included in Table 3. For the secondary endpoint of change in UACR from baseline to month 4, a relative reduction of 31.2% was observed in the Kerendia group compared to placebo. The

treatment effect for the primary and key secondary endpoints was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure (BP) and HbA1c at baseline.

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

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

treatment discontinuation. The initial decrease in eGFR was associated with long term preservation of kidney function.

Table 3: Analysis of the Primary and Secondary Time-to-Event Endpoints (and their Individual Components) in Phase III Study FIDELIO-DKD

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	Kerendia* 10 or 20 mg OD N=2833		**Placebo* N=2841**		**Treatment Effect Kerendia / Placebo**	
Primary and Secondary Time-to-event Endpoints:	**n (%)**	**Event Rate (100 pt–yr)**	**n (%)**	**Event Rate (100 pt–yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of kidney failure, sustained eGFR decline ≥40% or renal death	504 (17.8%)	7.59	600 (21.1%)	9.08	0.82 [0.73; 0.93]	0.0014
Kidney failure	208 (7.3%)	2.99	235 (8.3%)	3.39	0.87 [0.72; 1.05]	-
Sustained eGFR decline ≥40%	479 (16.9%)	7.21	577 (20.3%)	8.73	0.81 [0.72; 0.92]	-
Renal death	2 (<0.1%)	-	2 (<0.1%)	-	-	-
Secondary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization 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]	-
Hospitalization for heart failure	139 (4.9%)	1.89	162 (5.7%)	2.21	0.86 [0.68;1.08]	-
All-cause mortality	219 (7.7%)	2.90	244 (8.6%)	3.23	0.90 [0.75; 1.07]	0.2348**
All-cause hospitalization	1263 (44.6%)	22.56	1321 (46.5%)	23.87	0.95 [0.88; 1.02]	-
Kidney failure, sustained eGFR decline ≥ 57% or renal death	252 (8.9%)	3.64	326 (11.5%)	4.74	0.76 [0.65; 0.90]	-

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

** Not significant

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

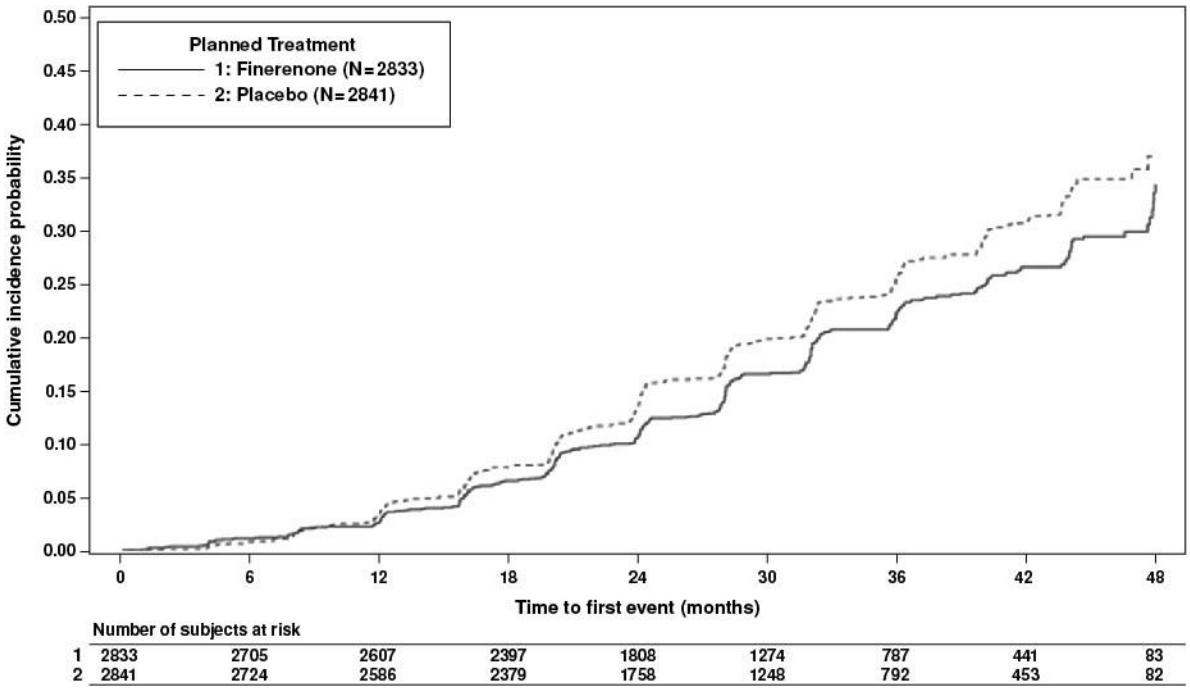


Figure 2: Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure in the FIDELIO-DKD study

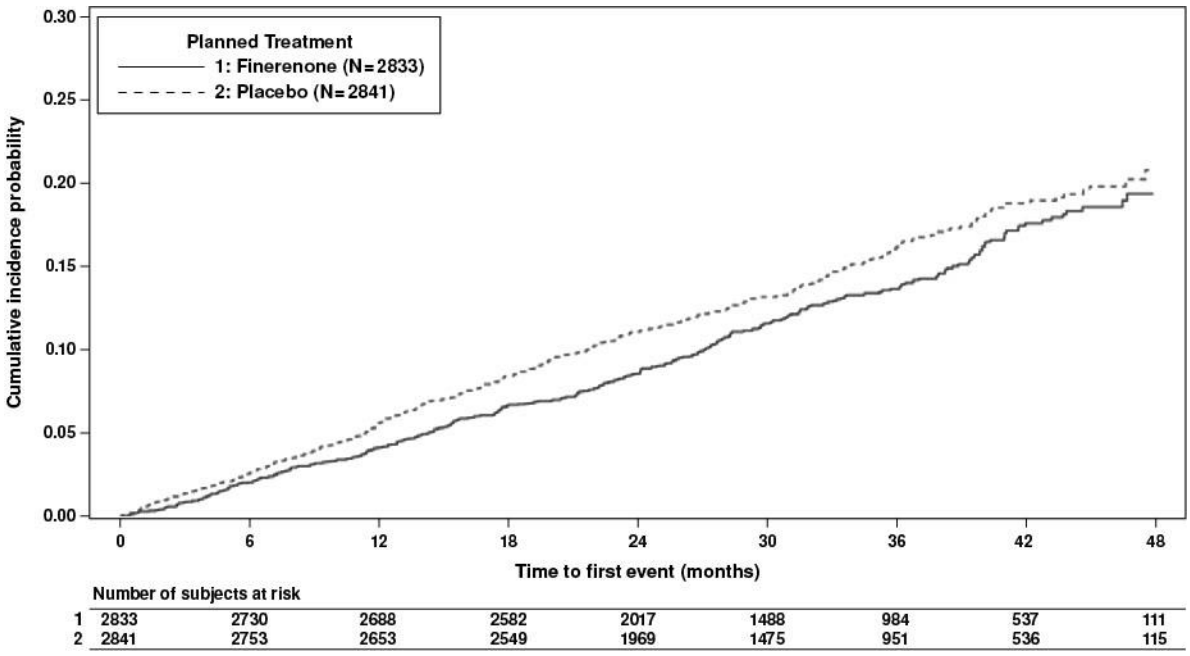


Figure 3: Primary renal composite outcomes according to subgroups

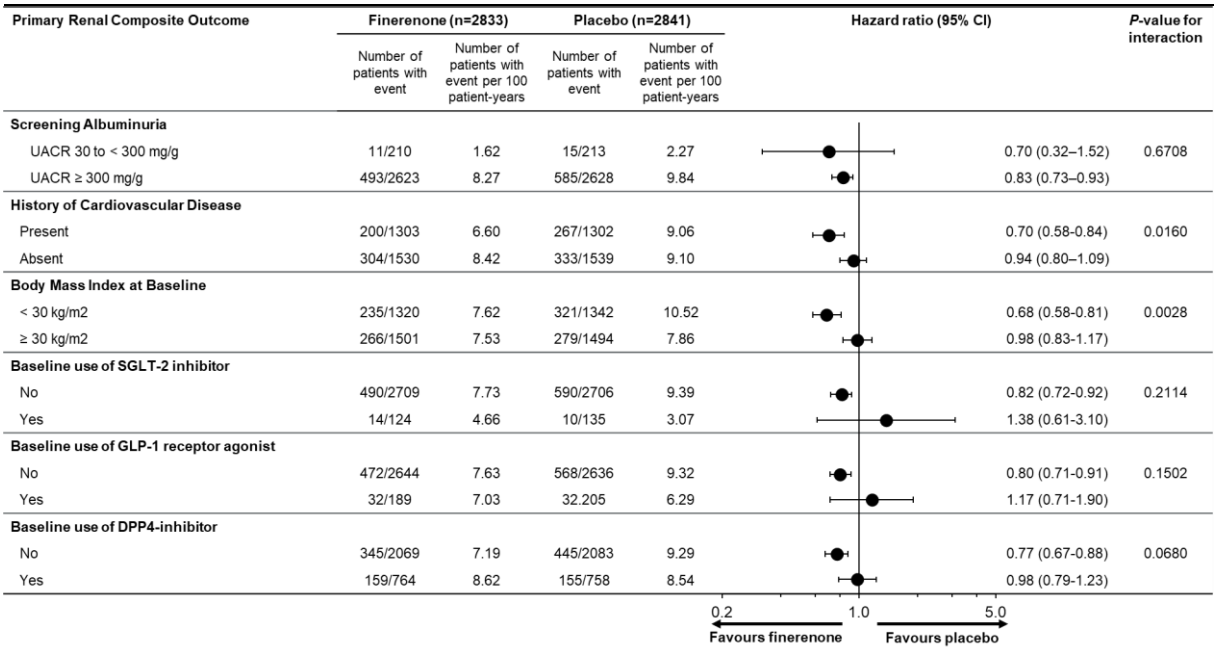
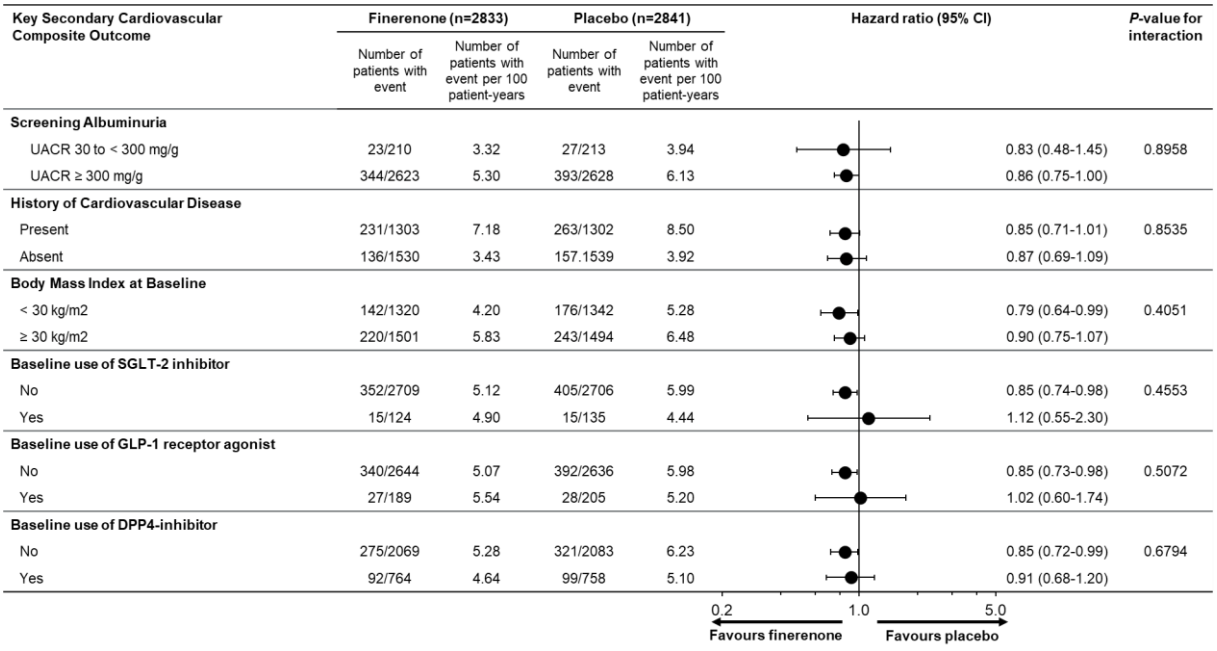


Figure 4: Secondary cardiovascular composite outcome according to subgroups



5.2 Pharmacokinetic properties

5.2.1 Pharmacokinetic / Pharmacodynamic relationships

The concentration-effect relationship over time for UACR was characterized by a maximum effect model indicating saturation at high exposures. The model-predicted time to reach the full (99%)

steady-state drug effect on UACR was 138 days. The pharmacokinetic (PK) half-life was 2-3 hours and PK steady state was achieved after 2 days, indicating timescale separation.

5.2.2 Absorption

Finerenone is almost completely absorbed after oral administration. Absorption is rapid with maximum plasma concentrations (C_{max}) appearing between 0.5 and 1.25 hours after tablet intake in the fasted state. The absolute bioavailability of finerenone is 43.5% due to first-pass metabolism in the gut-wall and liver. Finerenone is not a substrate of the efflux transporter P-gp in vivo. Intake with ≥high fat, high calorie food increased finerenone AUC by 21%, reduced C_{max} by 19% and prolonged the time to reach C_{max} to 2.5 hours. This is not clinically relevant. Therefore, finerenone can be taken with or without food *(see section 'Dosage and method of administration')*.

5.2.3 Distribution

The volume of distribution at steady state (Vss) of finerenone is 52.6 L. The human plasma protein binding of finerenone *in vitro* is 91.7%, with serum albumin being the main binding protein.

5.2.4 Metabolism / Biotransformation

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. Four major metabolites were found in plasma, resulting from oxidation of the dihydropyridine moiety to a pyridine (M1a, M1b), subsequent hydroxylation of a methyl group (M2a) and formation of a carboxyl function (M3a). All metabolites are pharmacologically inactive.

5.2.5 Elimination / Excretion

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

5.2.6 Linearity / Non-linearity

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

5.2.7 Additional information on special populations

5.2.7.1 Patients with renal impairment

Mild renal impairment (CL_{CR} 60 - < 90 mL/min) did not affect finerenone AUC and C_{max}. Compared to subjects with normal renal function (CLCR ≥ 90 mL/min), the effect of moderate (CL_{CR} 30 - < 60 mL/min) or severe (CL_{CR} < 30 mL/min) renal impairment on AUC of finerenone was

similar with increases by 34-36%. Moderate or severe renal impairment had no effect on C_{max} *(see section* 'Dosage and method of administration*).*

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

5.2.7.2 Patients with hepatic impairment

There was no change in finerenone exposure in cirrhotic subjects with mild hepatic impairment (Child Pugh A) *(see section* 'Dosage and method of administration'*).*

In cirrhotic subjects with moderate hepatic impairment (Child Pugh B), finerenone mean AUC was increased by 38% and C_{max} was unchanged compared to healthy control subjects *(see section* 'Dosage and method of administration*).*

There are no data in patients with severe hepatic impairment (Child Pugh C) *(see section* 'Dosage and method of administration' *and* 'Special warnings and precautions for use'*).*

5.2.7.3 Geriatric patients

Of the 2827 patients who received Kerendia in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Elderly subjects (≥ 65 years of age) exhibited higher finerenone plasma concentrations than younger subjects (≤ 45 years of age), with mean AUC and C_{max} values being 34% and 51% higher in the elderly *(see section* 'Dosage and method of administration*')*. [13]

Population-pharmacokinetic analyses did not identify age as a covariate for finerenone AUC or C_{max}.

5.2.7.4 Gender

Gender had no effect on the pharmacokinetics of finerenone *(see section* 'Dosage and method of administration'*).*

5.2.7.5 Body Weight

Population-pharmacokinetic analyses identified body weight as a covariate for finerenone C_{max}. The C_{max} of a subject with a body weight of 50 kg was estimated to be 43% to 51% higher compared to a subject of 100 kg. Dose adaptation based on body weight is not warranted *(see section* 'Dosage and method of administration'*).*

5.2.7.6 Ethnic differences

Population-pharmacokinetic analyses in patients demonstrated no clinically relevant difference in finerenone exposure between Asian and Caucasian patients *(see section* 'Dosage and method of administration'*).*

5.2.7.7 Smoking status

Finerenone is not metabolized by an enzyme that is inducible by tobacco smoke *(see section* 'Dosage and method of administration*).*

5.3 Preclinical safety data

5.3.1 Embryotoxicity / Teratogenicity

In the embryo-fetal toxicity in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans. At 30 mg/kg/day, the

incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for AUCunbound. Therefore, the findings in rats do not indicate an increased concern for fetal harm *(see section*` Fertility, pregnancy and lactation'*).*

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$. The increased locomotor activity in offspring may indicate a potential risk for the fetus. In addition, because of the findings in pups, a risk for the nursing infant cannot be excluded *(see section* 'Special warnings and precautions for use' *and*` Fertility, pregnancy and lactation'*).*

5.3.2 Reproduction toxicity

Male fertility was not affected by Kerendia *(see section*` Fertility, pregnancy and lactation'*).*

Finerenone caused reduced female fertility (decreased number of corpora lutea and implantation sites) as well as signs of early embryonic toxicity (increased post-implantational loss and decreased number of viable fetuses) at about 21 times the human $AUC_{unbound}$. In addition, reduced ovarian weights were found at about 17 times the human $AUC_{unbound}$. No effects on female fertility and early embryonic development were found at 10 times the human $AUC_{unbound}$. Therefore, the findings in female rats are of little clinical relevance *(see section*` Fertility, pregnancy and lactation'*).*

5.3.3 Genotoxicity and carcinogenicity

Finerenone was non-genotoxic in an in vitro bacterial reverse mutation (Ames assay), the in vitro chromosomal aberration assay and the in vivo micronucleus assay.

In 2-year carcinogenicity studies, finerenone did not show a carcinogenic potential in Wistar rats as well as CD1 mice. In male mice, finerenone resulted in an increase in Leydig cell adenoma at doses representing 26 times the $AUC_{unbound}$ in humans. A dose representing 17 times the $AUC_{unbound}$ in humans did not cause any tumors. Based on the known sensitivity of rodents to develop these tumors and the pharmacology-based mechanism at supratherapeutic doses as well as adequate safety margins, the increase in Leydig cell tumors in male mice is not clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline (E 460)
Croscarmellose sodium
Hypromellose 5 cP (E 464)
Lactose monohydrate
Magnesium stearate (E 470b)
Sodium laurilsulfate (E 487)

Tablet coating:
Ferric oxide red (E 172) (Kerendia 10 mg film-coated tablet)
Ferric oxide yellow (E 172) (Kerendia 20 mg film-coated tablet)
Hypromellose 5 cP (E 464)
Talc (E 553 b)
Titanium dioxide (E 171)

6.2 Incompatibilities

N/A

6.3 Shelf life

Please refer to labels

6.4 Special precautions for storage

Store below 30 °C

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Instructions for use / handling

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

7 PRODUCT REGISTRANT

Bayer (South East Asia Pte Ltd)
2 Tanjong Katong Road #07-01, Paya Lebar Quarter 3 Singapore 437161

8 DATE OF LAST REVISION

October 2021