Drug Monograph

Drug Name:	**Kerendia® (finerenone) tablet**
Drug Class:	**Cardiovascular: Non-Steroidal Mineralocorticoid Receptor Antagonist (MRA)**
Prepared For:	MO HealthNet
Prepared By:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Kerendia is available in 10 mg and 20 mg tablets.
Manufacturer:	Distributed by: Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ 07981.
Summary of Findings:	FDA approval of Kerendia was based on the results of the Phase 3, randomized, double-blind, placebo-controlled FIDELIO-DKD trial, in which 5,674 adult patients were included in the statistical analysis. Eligible participants had the diagnoses of chronic kidney disease and type 2 diabetes mellitus and were randomized 1:1 to receive Kerendia or placebo. The study consisted of a run-in period (4 to 16 weeks), screening (≤ 2 weeks), and a double-blind treatment period. At the conclusion of the study, patients had been followed for 2.2 years. The primary composite outcome of kidney failure, sustained decrease of ≥ 40 % in estimated glomerular filtration rate from baseline, or death from renal causes was significantly lower in the Kerendia group (17.8%) versus the placebo group (21.1%). Patients in the Kerendia group also showed a lower relative risk of secondary cardiovascular outcomes when compared to the placebo group.
Status Recommendation:	☒ Clinical Edit ☐ Open Access ☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required ☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2,3]

Approximately 8 million people in the United States (U.S.) have concurrent diagnoses of type 2 diabetes mellitus (T2D) and chronic kidney disease (CKD). CKD is defined as persistently elevated urine albumin excretion (≥ 30 mg/g creatinine), persistently reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73m^2), or both for 3 or more months. The prevalence of CKD among adult type 2 diabetic patients is 37%. Around 50% of CKD patients also have a diagnosis of diabetes or cardiovascular disease (CVD). In patients with T2D, mineralocorticoid receptor (MR) overactivation is thought to contribute to fibrosis and inflammation which can lead to permanent kidney damage. CKD is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage. Progression can lead to end-stage renal disease (ESRD) requiring dialysis or kidney transplant and is the leading cause of ESRD in the U.S. Stages 1–2 CKD are defined by evidence of high albuminuria with eGFR ≥ 60 mL/min/1.73 m^2, while stages 3–5 CKD are defined by progressively lower ranges of eGFR. Stage 5 CKD is also denoted as kidney failure. At any eGFR, the degree of albuminuria is associated with risk of CVD, CKD progression, and mortality. Based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions.

Dosage Form [4]

Kerendia is available in 10 mg and 20 mg tablets.

Manufacturer [4]

Distributed by: Bayer Healthcare Pharmaceuticals, Inc., Whippany, NJ 07981.

Indication(s) [4]

Kerendia is indicated to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction (MI), and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Kerendia is a non-steroidal, selective antagonist of the mineralocorticoid receptor (MR), which is activated by aldosterone and cortisol and regulates gene transcription. Kerendia blocks MR mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart and blood vessels) tissues. MR overactivation is thought to contribute to fibrosis and inflammation. Kerendia has a high potency and selectivity for the MR and has no relevant affinity for androgen, progesterone, estrogen, and glucocorticoid receptors.

Pharmacokinetics:

Bioavailability	44%
Metabolism	Hepatic (CYP3A4 – 90%; CYP2C8 – 10%)
Excretion	Renal (80%); Fecal (20%)
Half-life	2-3 hours

Clinical Trials Experience

STUDY DESIGN (FIDELIO-DKD; NCT02540993)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven Phase 3 study
INCLUSION CRITERIA	• Adults ≥ 18 years of age • Type 2 diabetes mellitus (T2D) as defined by the American Diabetes Association • Diagnosis of CKD with at least one of the following criteria at run-in and screening visits: ○ Persistent high albuminuria [Urinary Albumin-to-Creatinine Ratio (UACR) ≥ 30 to < 300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥ 25 but < 60 mL/min/1.73m^2 (CKD EPI) and the presence of diabetic retinopathy ○ Persistent very high albuminuria (UACR ≥ 300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥ 25 to < 75 mL/min/1.73m^2 (CKD EPI) • Prior standard of care treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) as follows: ○ For at least 4 weeks prior to the run-in visit, subjects should be treated with only an ACEI or ARB, or both ○ Starting with the run-in visit, subjects should be treated with only an ACEI or ARB ○ For at least 4 weeks prior to screening visit, subjects should be treated with the maximum tolerated labeled dose (but not below the minimal labeled dose) of only an ACEI or an ARB (not both) preferably without any adjustments to dose or choice of agent or to any other antihypertensive or antiglycemic treatment • Serum potassium ≤ 4.8 mmol/L at both the run-in and the screening visit
EXCLUSION CRITERIA	• Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis • Uncontrolled hypertension (i.e., mean sitting systolic blood pressure [SBP] ≥ 170 mmHg, sitting diastolic blood pressure [DBP] ≥ 110 mmHg at run-in visit, or mean sitting SBP ≥ 160 mmHg, sitting DBP ≥ 100 mmHg at screening) • Glycated hemoglobin (HbA1c) > 12% • Mean SBP < 90 mmHg at the run-in visit or at the screening visit • Clinical diagnosis of chronic heart failure with reduced ejection fraction (HFrEF) and persistent symptoms (New York Heart Association (NYHA) class II-IV) at run-in visit (class 1A recommendation for mineralocorticoid receptor antagonists [MRAs]) • Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last

	30 days prior to the screening visit • Dialysis for acute renal failure within 12 weeks of the run-in visit • Renal allograft in place or scheduled within the next 12 months for the run-in visit
TREATMENT REGIMEN	A total of 5,674 patients were randomized to receive Kerendia (N=2,833) or placebo (N=2,841) and were followed for a median of 2.6 years. The starting dose of Kerendia was based on screening eGFR (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 ≥ 60 mL/min/1.73 m^2). The dose of Kerendia could be titrated during the study, with a target dose of 20 mg daily.
RESULTS	The primary endpoint was a composite of kidney failure (defined as end-stage kidney disease or eGFR < 15 mL/min/1.73 m^2), a sustained decline in eGFR of ≥ 40% from baseline over a period of ≥ 4 weeks), or death from renal causes. End-stage kidney disease was defined as initiation of long-term dialysis (for ≥ 90 days) or kidney transplantation. The key secondary outcome was composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. **Analysis of Primary and Secondary Efficacy Outcomes in FIDELIO-DKD**

	Kerendia (N=2,833)		**Placebo (N=2,841)**		**Treatment Effect Kerendia/Placebo**	
	n (%)	Event Rate (100 pt-yr)	n (%)	Event Rate (100 pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Time-to-Event Endpoints						
Composite of kidney failure, sustained eGFR decline ≥ 40% or renal death	504 (17.8%)	7.6	600 (21.1%)	9.1	0.82 [0.73-0.93]	0.001
Kidney failure	208 (7.3%)	3.0	235 (8.3%)	3.4	0.87 [0.72-1.05]	-
Sustained eGFR decline ≥ 40%	479 (16.9%)	7.2	577 (20.3%)	8.7	0.81 [0.72-0.92]	-
Renal death	2 (<0.1%)	-	2 (<0.1%)	-	-	-
Secondary Time-to-Event Endpoints						
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure	367 (13.0%)	5.1	420 (14.8%)	5.9	0.86 [0.75-0.99]	0.034
CV death	128 (4.5%)	1.7	150 (5.3%)	2.0	0.86 [0.68-1.08]	-
Non-fatal MI	70 (2.5%)	0.9	87 (3.1%)	1.2	0.80 [0.58-1.09]	-
Non-fatal stroke	90 (3.2%)	1.2	87 (3.1%)	1.2	1.03 [0.76-1.38]	-
Hospitalization for heart failure	139 (4.9%)	1.9	162 (5.7%)	2.2	0.86 [0.68-1.08]	-

	Abbreviations: CI = confidence interval, N = number of subjects, n = number of subjects with event, pt-yr = patient year. NOTE: For patients with multiple events, only the first event contributed to the composite endpoint. Sums of the numbers of first events for the single components do not add up to the numbers of events in the composite endpoint. The primary composite endpoint was statistically lower in the Kerendia group (17.8%) versus the placebo group (21.1%). Also, patients who received Kerendia had a lower relative risk of key secondary outcome events, occurring in 13% of patients in the Kerendia group and 14.8% of patients in the placebo group.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications (4)

- Concomitant use with strong CYP3A4 inhibitors
- Patients with adrenal insufficiency

Warnings and Precautions (4)

- Hyperkalemia – Patients with decreased kidney function and higher baseline potassium levels are at increased risk. Monitor serum potassium levels and adjust dose as needed.

Adverse Effects (4)

Most common, ≥ 1%	Kerendia (N=2,827) n (%)	Placebo (N=2,831) n (%)
Hyperkalemia	516 (18.3)	255 (9.0)
Hypotension	135 (4.8)	96 (3.4)
Hyponatremia	40 (1.4)	19 (0.7)

Drug Interactions (4)

- Strong CYP3A4 Inhibitors: Use is contraindicated.
- Grapefruit or grapefruit juice: Avoid concomitant use.
- Moderate or weak CYP3A4 Inhibitors: Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate.
- Strong of moderate CYP3A4 Inducers: Avoid concomitant use.

Dosage and Administration (4)

The recommended starting dose of Kerendia is based on eGFR and is presented in the table below:

Recommended Starting Dose	
eGFR (mL/min/1.73m^2)	**Starting Dose**
≥ 60	20 mg once daily
≥ 25 to < 60	10 mg once daily
< 25	Not Recommended

- The target daily dose of Kerendia is 20 mg.
- Measure serum potassium 4 weeks after initiating treatment and any dosage adjustments.
- Dose adjustment is based on current serum potassium concentrations and current Kerendia dose. See table below.

Dose Adjustment Based on Current Serum Potassium Concentration and Current Dose			
		Current Kerendia Dose	
		10 mg once daily	20 mg once daily
Current Serum Potassium (mEq/L)	≤ 4.8	Increase dose to 20 mg once daily*	Maintain 20 mg once daily
	> 4.8-5.5	Maintain 10 mg once daily	Maintain 20 mg once daily
	> 5.5	Withhold Kerendia. Consider restarting at 10 mg once daily when serum potassium ≤ 5.0 mEq/L	Withhold Kerendia. Restart at 10 mg once daily when serum potassium ≤ 5.0 mEq/L

* If eGFR has decreased by more than 30% compared to previous measurement, maintain 10 mg dose.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Finerenone	Kerendia®	Bayer	20 mg orally once daily	$569.10, at 20 mg once daily
Eplerenone	Inspra®	Pfizer	25 mg orally once daily or 50 mg orally once or twice daily	$104.10, at 50 mg once daily

** Wholesale Acquisition Cost

Conclusion

The prevalence of CKD among adult type 2 diabetic patients is 37%. Around 50% of CKD patients also have a diagnosis of diabetes or cardiovascular disease (CVD). In patients with T2D, mineralocorticoid receptor (MR) overactivation is thought to contribute to fibrosis and inflammation which can lead to permanent kidney damage. Kerendia blocks MR mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart and blood vessels) tissues. FDA approval of Kerendia was based on the results of the FIDELIO-DKD trial, in which eligible participants with diagnoses of chronic kidney disease and type 2 diabetes mellitus were randomized 1:1 to receive Kerendia or placebo. The primary composite outcome of kidney failure, sustained decrease of ≥ 40% in estimated glomerular filtration rate from baseline, or death from renal causes was significantly lower in the Kerendia group (17.8%) versus the placebo group (21.1%). Patients in the Kerendia group also showed a lower relative risk of secondary cardiovascular outcomes when compared to the placebo group. Although Kerendia will compete with the sodium-glucose co-transporter 2 (SGLT2) inhibitors for the indication of CKD in patients with T2D, the currently higher cost and more narrow indication will be the largest factors in the level of management in coverage determination for this product.

Recommendation

The MO Healthnet Division recommends adding this drug to a new Kerendia clinical edit.

References

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4) Kerendia [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; July 2021.
5) Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G; FIDELIO-DKD Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020 Dec 3;383(23):2219-2229. doi: 10.1056/NEJMoa2025845. Epub 2020 Oct 23.

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