Finerenone (KERENDIA) National Drug Monograph April 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) that blocks sodium reabsorption, and mineralocorticoid receptor overactivation in the kidney as well as the heart and blood vessels. Per the product information, mineralocorticoid receptor overactivation is thought to contribute to fibrosis and inflammation. Finerenone has a high potency and selectivity for the mineralocorticoid receptor and has no relevant affinity for androgen, progesterone, estrogen, and glucocorticoid receptors.

Indication(s) Under Review in This Document

- Finerenone 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 hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes.

Dosage Form(s) Under Review

- Finerenone is available as 10 mg and 20 mg tablets. The recommended starting dose is 10 mg or 20 mg orally once daily, taking into consideration eGFR and serum potassium. The dose may be increased after 4 weeks to the target dose of 20 mg once daily, based on eGFR and serum potassium thresholds. Refer to product information.

Clinical Evidence Summary[1-3]

Efficacy Considerations[1-3]

- Data for approval of finerenone is based primarily on Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD), a phase 3 randomized, double-blind, placebo-controlled trial. In this study, patients with type 2 diabetes mellitus (T2DM) and CKD receiving maximally tolerated doses of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) were randomized to treatment with finerenone (10 mg or 20 mg based on eGFR) or placebo. The median follow-up was 2.6 years.[2]
- Inclusion criteria for CKD was defined as: persistent, moderately elevated albuminuria (urinary albumin-to-creatinine ratio [UACR] 30 to < 300 mg/g), an eGFR 25 to < 60 ml/min/1.73m2, and a history of diabetic retinopathy; or persistent, severely elevated albuminuria (UACR 300 to 5000 mg/g) and an eGFR 25 to < 75 ml/min/1.73m2. At screening, patients were required to have a serum potassium 4.8 mmol/L or less. Treatment was withheld if the potassium increased above 5.5 mmol/L and restarted when potassium decreased to 5.0 mmol/L or less. In addition to other exclusion criteria, patients with uncontrolled hypertension, heart failure with reduced ejection fraction, or hepatic insufficiency (Child-Pugh C) were excluded from the trial.
- The primary outcome of FIDELIO-DKD was a composite of kidney failure (end-stage kidney disease [ESKD] or an eGFR < 15 ml/min/1.73m2), a sustained decrease in eGFR of at least 40% from baseline over a timeframe of at least 4 weeks, or death from renal causes. End-stage kidney disease was defined as the initiation of long-term dialysis (90 days or more) or kidney transplantation. Results of the primary outcome are included in Table 1 below.

Table 1: Primary outcome results in FIDELIO-DKD[2]

FIDELIO-DKD	Finerenone N=2833	Placebo N=2841
Composite primary outcome	504 (17.8%)	600 (21.1%)
HR (95% CI)	0.82 (0.73 to 0.93); P=0.001	
Components of the primary outcome		
Kidney failure	HR 0.87 (95% CI 0.72 to 1.05)	
Sustained decrease >= 40% eGFR from baseline	HR 0.81 (95% CI 0.72 to 0.92)	
Death from renal causes	2 (< 0.1%)	2 (< 0.1%)

HR=Hazard Ratio; CI=Confidence Interval

- The key secondary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure was significantly reduced with finerenone vs. placebo (HR 0.86; 95% CI 0.75 to 0.99; P=0.03). The individual components of the composite key secondary outcome were numerically lower with finerenone compared to placebo (except nonfatal stroke); although, the differences were not statistically significant. There was no significant difference between finerenone and placebo in the secondary outcome of all-cause mortality.
- According to the trial results, 98.1% and 98.8% of patients were treated with maximally tolerated labeled doses of an ACEI or ARB, respectively. Adherence to study treatment was approximately 92%, with a mean dose of 15.1 mg in the finerenone treatment group and 16.5 mg in the placebo group. At the conclusion of the trial, 29.0% of patients in the finerenone group discontinued treatment compared to 28.2% of patients on placebo.
- Another clinical trial, Finerenone in Reducing Cardiovascular Morbidity and Mortality in Diabetic Kidney Disease (FIGARO-DKD) randomized 7437 patients with persistent, moderately elevated albuminuria (UACR 30 to < 300 mg/g) and an eGFR 25 to 90 ml/min/1.73m2, or persistent, severely elevated albuminuria (UACR 300 to 5000 mg/g) and an eGFR of at least 60 ml/min/1.73m2 to treatment with finerenone (10 mg or 20 mg based on eGFR) or placebo for a median duration of follow-up of 3.4 years. Patients were also required to have a serum potassium 4.8 mmol/L or less at screening. The primary composite outcome of FIGARO-DKD (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure) was significantly reduced in patients on finerenone (12.4%) compared to placebo (14.2%) (HR 0.87; 95% CI 0.76 to 0.98; P=0.03). The difference in the first secondary outcome of a composite first occurrence of kidney failure, sustained decrease from baseline of at least 40% in eGFR for at least 4 weeks, or death from renal causes was not significant between treatment with finerenone vs. placebo.[3]

Safety Results from Clinical Trials[1-3]

- In FIDELIO-DKD, serious adverse reactions occurred in 31.9% of patients on finerenone compared to 34.3% of patients in the placebo group. Discontinuation due to adverse reactions were reported in 7.3% of patients on finerenone and 5.9% of patients receiving placebo. Discontinuation due to hyperkalemia occurred in 2.3% of patients treated with finerenone vs. 0.9% on placebo. Acute kidney injury related adverse events were reported in 4.6% of patients on finerenone compared to 4.8% on placebo. In FIGARO-DKD, hyperkalemia was reported in 10.8% of patients on finerenone vs. 5.3% on placebo.
- The most common adverse events reported in FIDELIO-DKD and as noted in the product information are included in Table 2 below.

Table 2: Adverse reactions reported in >=1% on finerenone and more frequently than placebo[1,2]

Adverse Reactions[a]	Finerenone N=2827	Placebo N=2831
Hyperkalemia	516 (18.3%)	255 (9.0%)
Hypotension	135 (4.8%)	96 (3.4%)
Hyponatremia	40 (1.4%)	19 (0.7%)

[a] most common adverse drug reactions

Safety Considerations[1]

- **Boxed warning:** None.
- **Contraindications:**
  - Concomitant use with strong CYP3A4 inhibitors
  - Patients with adrenal insufficiency
- **Warnings / precautions**:
  - Hyperkalemia: Patients with decreased kidney function and higher baseline potassium levels are at increased risk. Do not initiate finerenone if serum potassium is > 5.0 mEq/L. Monitor serum potassium levels and adjust dose as needed.

Other Considerations[1-13]

- Drug interactions: finerenone is a CYP3A4 substrate and is contraindicated with strong CYP3A4 inhibitors due to the increase in finerenone exposure and potential increase in adverse reactions. Concomitant intake of grapefruit or grapefruit juice should also be avoided. If finerenone is used concomitantly with moderate or weak CYP3A4 inhibitors, it is recommended to monitor serum potassium during drug initiation or dosage adjustment of finerenone or the moderate or weak CYP3A4 inhibitor and adjust the dose of finerenone as indicated. In addition, concomitant use of finerenone with a strong or moderate CYP3A4 inducer should be avoided due to decreases in finerenone exposure which may reduce the efficacy of finerenone. It is also recommended to monitor serum potassium more frequently in patients receiving concomitant therapy with drugs or supplements that increase serum potassium.[1]
- Finerenone is a nonsteroidal MRA that is reported to be more selective for the mineralocorticoid receptor than other steroid receptors (i.e., glucocorticoid receptor, androgen receptor, progesterone receptor). This is thought to contribute to a potential lower rate of side effects compared to other MRAs including spironolactone (non-selective MRA) and eplerenone (selective MRA).[4] In direct comparison data from a phase II clinical trial of patients with heart failure and CKD, 4.5% of patients on finerenone 10 mg once daily and 7.8% of patients on finerenone 5 mg twice daily experienced an adverse event of hyperkalemia or increased potassium compared to 11.1% of patients on spironolactone 25 or 50 mg once daily.[5] In a phase IIb trial of patients with heart failure and diabetes and/or CKD, an increase in potassium >= 5.6 mmol/L was noted in 4.7% of patients in the eplerenone group (25 mg every other day, titrated to 50 mg daily) compared to 3.6% of patients on finerenone 10 mg titrated to 20 mg once daily, and 6.3% in the treatment group on finerenone 15 mg titrated to 20 mg once daily.[6] Direct comparison data from Phase 3 trials at the recommended doses of the available MRAs are needed to confirm any difference in rates of hyperkalemia or other adverse events.[4]
- Data with spironolactone or eplerenone added to an ACEI or ARB in preventing the progression of CKD or death in patients with proteinuria are uncertain due to limited data on the long-term outcome benefit. According to a Cochrane review (conducted prior to the publication of FIDELIO-DKD and FIGARO-DKD), the addition of an MRA to an ACEI or ARB may reduce proteinuria, eGFR and systolic blood pressure in patients with mild to moderate CKD, with the potential for increased adverse effects including hyperkalemia, acute kidney injury, and gynecomastia.[4] Direct comparison data in Phase 3 outcome trials are needed to establish place in therapy of finerenone vs. other available MRAs in the management of patients with T2DM and CKD with proteinuria.
- Patients with heart failure with reduced ejection fraction were excluded from FIDELIO-DKD[2] and FIGARO-DKD,[3] noting that use of an MRA is a Class IA recommendation per heart failure guidelines based on data with spironolactone and eplerenone.[7]

- It was noted that in FIDELIO-DKD and FIGARO-DKD, there was only a modest blood pressure lowering effect with finerenone compared to placebo (systolic blood pressure -3.0 mm Hg at 1 year, -2.6 mm Hg at 2 years, respectively). In addition, patients with uncontrolled hypertension were excluded from these trials.[2,3] Both eplerenone and spironolactone are approved for use in the management of hypertension and have been used in the treatment of resistant hypertension.[8] Finerenone does not have approval for use in the management of hypertension.[1]
- In addition to their benefit in the management of T2DM, a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended in patients with CKD and T2DM for their renoprotective and cardioprotective effects.[9,10] Treatment with an SGLT2 inhibitor significantly reduced the primary outcome of ESKD, sustained decline in eGFR, or death from renal or cardiovascular causes compared to placebo by 30% in patients with T2DM and nephropathy[11] and by 39% in patients with CKD and proteinuria with or without T2DM.[12] These trials enrolled patients receiving maximally tolerated doses of an ACEI or ARB.[11,12] The clinical outcome trials with finerenone in T2DM and CKD also enrolled patients on maximally tolerated doses of an ACEI or ARB, with only 4.6% (FIDELIO-DKD)[2] and 8.4% (FIGARO-DKD)[3] of patients receiving an SGLT2 inhibitor at baseline. Based on subgroup analysis, patients in the finerenone group who were receiving an SGLT2 inhibitor at baseline did not demonstrate benefit in the primary composite renal outcome compared to placebo in FIDELIO-DKD.[2] In FIGARO-DKD, the subgroup of patients on an SGLT2 inhibitor at baseline did show benefit in the primary composite cardiovascular outcome with finerenone compared to placebo.[3] When the data from FIDELIO-DKD and FIGARO-DKD were pooled, it was noted that the results for the composite cardiovascular endpoint were consistent in the prespecified subgroup of whether or not patients were on an SGLT2 inhibitor at baseline.[13] Direct comparison data, or data evaluating concomitant therapy are needed to clearly establish place in therapy of finerenone and/or an SGLT2 inhibitor in patients with T2DM and CKD with proteinuria. Recent clinical practice guidelines have recommended finerenone to reduce CKD progression and cardiovascular events in patients with CKD who are at increased risk for cardiovascular events or CKD progression or are unable to use an SGLT2 inhibitor.[10]

Other Therapeutic Options[1-12]

A comparison of finerenone to other MRAs or SGLT2 inhibitors available on the VA National Formulary are listed in Table 3 below.

Table 3 Comparison of available MRAs, and selected SGLT2 inhibitors

Treatment	Formulary status	Clinical Guidance	Other Considerations
Finerenone	NF (CFU)	FDA indication(s): CKD with T2DM CKD or DM related guidelines: -Finerenone is recommended to reduce CKD progression and CV events in patients with CKD who are at increased risk for CV disease progression or CKD progression or are unable to use an SGLT2 inhibitor[10]	Nonsteroidal, selective MRA Most common adverse reactions: hyperkalemia, hypotension, hyponatremia Warnings/Precautions: hyperkalemia Contraindicated with concomitant use of strong CYP3A4 inhibitors
Spironolactone	VANF	FDA indication(s): Hypertension, HFrEF, primary hyperaldosteronism, edema in cirrhosis and nephrotic syndrome	Non-selective MRA Most common adverse reactions: gynecomastia Warnings/Precautions: hyperkalemia, hypotension and worsening renal function, electrolyte and metabolic abnormalities, gynecomastia
Eplerenone	VANF (PA-F)	FDA indication(s): Hypertension, heart failure post MI	Selective MRA Most common adverse reactions: hyperkalemia, increased creatinine Warnings/Precautions: hyperkalemia Contraindicated with concomitant use of strong CYP3A4 inhibitors
Empagliflozin	VANF	FDA indication(s): T2DM, HF CKD or DM related guidelines: -An SGLT2 inhibitor is recommended in patients with T2DM, CKD and eGFR >= 30[9] -An SGLT2 inhibitor is recommended in T2DM and DKD in patients with eGFR >= 25 and UACR >=300 to reduce CKD progression and CV events; consider use for CV risk reduction when eGFR and UACR are >=25 or >= 300, respectively[10]	SGLT2 inhibitor Most common adverse reactions: urinary tract infections, female genital mycotic infections Warnings/Precautions: ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum, genital mycotic infections, hypersensitivity reactions

CFU=criteria for use; CV=cardiovascular; eGFR=estimated glomerular filtration rate (ml/min/1.73m2); DKD=diabetic kidney disease; FDA=U.S. Food and Drug Administration; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MI=myocardial infarction; NF=non-formulary; PA-F=prior authorization at the facility level; UACR=urinary-to-albumin creatinine ratio (mg/g); VANF=VA National Formulary

Projected Place in Therapy[1-12]

- Type 2 diabetes is noted to affect approximately 25% of patients receiving care in VA and is linked to kidney disease including nephropathy and end-stage kidney disease. Clinical practice guideline recommendations include the use of an ACEI or ARB in patients with diabetes, hypertension and albuminuria for their benefit in slowing CKD progression and reducing cardiovascular events.[9,10] In addition, guidelines recommend an SGLT2 inhibitor in patients with T2DM and chronic kidney disease to reduce progression of kidney disease and cardiovascular events.[9,10] Although a nonselective MRA in addition to renin-angiotensin aldosterone blockade has been to shown to reduce proteinuria in patients with CKD and albuminuria, data have been limited on the clinical outcome benefit with an MRA in addition to an ACEI or ARB.[4,9]

- More recently, the nonsteroidal MRA finerenone demonstrated an 18% reduction in the primary composite outcome of kidney failure, sustained decrease in eGFR, or death from renal causes compared to placebo in patients with more advanced diabetic kidney disease.[2] In a second clinical trial of patients with T2DM and earlier stage CKD, finerenone reduced the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure by 13% compared to placebo.[3] In both trials, patients were receiving therapy with an ACEI or ARB at maximally tolerated labeled doses. Hyperkalemia was reported in patients receiving finerenone at approximately twice the rate compared to patients in the placebo group.[2,3] As finerenone was compared to placebo in these trials rather than another MRA, differences in clinical outcomes or side effects in patients with diabetic kidney disease remain to be determined.
- An SGLT2 inhibitor is another class of agents that has demonstrated cardiorenal outcome benefit. Only 4.6% of patients in FIDELIO-DKD[2] and 8.4% of patients in FIGARO-DKD[3] were receiving treatment with an SGLT2 inhibitor. In clinical outcome trials, treatment with an SGLT2 inhibitor significantly reduced the primary outcome of end-stage kidney disease, sustained decline in eGFR, or death from renal or cardiovascular causes compared to placebo by 30% in patients with T2DM and nephropathy[11] and by 39% in patients with CKD and proteinuria with or without T2DM.[12] Clinical practice guidelines recommend an SGLT2 inhibitor in patients with T2DM and CKD (refer to Table 3 for specific language).[9,10] Guidelines have recommended finerenone to reduce CKD progression and cardiovascular events in patients with CKD who are at increased risk for cardiovascular events or CKD progression or are unable to use an SGLT2 inhibitor.[10]

References

1. KERENDIA (finerenone) tablets, for oral use [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals. July 2021.
2. Bakris GL, Agarwal R, Anker SD, et al., for the FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219-29.
3. Pitt B, Filippatos G, Agarwal R, et al., for the FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252-63.
4. Chung EYM, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev 2020, Issue 10. Art. No.: CD007004. DOI: 10.1002/14651858.CD007004.pub4.
5. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J 2013;34:2453-63.
6. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37:2105-14.
7. Yancy CW, Jessup M, Bozkurt B, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–e327.
8. Bazoukis G, Thomopoulos C, Tsioufis C. Effect of mineralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. J Hypertens 2018;36:987-94.
9. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98:S1–S115.
10. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45(Suppl 1):S175–S84.
11. Perkovic V, Jardine MJ, Neal B, et al., for the CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.
12. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al., for the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
13. Agarwal R, Filippatos G, Pitt B, et al.; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with Finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474-84.

Prepared February 2022. Contact person: Elaine Furmaga, PharmD, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (10P4P)