

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**215341Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	215341
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<b>OSE RCM #</b>	2020-2333
<b>Reviewer Name(s)</b>	Brian Caruth, Pharm.D., BCPS
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<b>Division Director</b>	Cynthia LaCivita, Pharm.D.
<b>Review Completion Date</b>	June 25, 2021
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Finerenone
<b>Trade Name</b>	Kerendia
<b>Name of Applicant</b>	Bayer HealthCare Pharmaceuticals, Inc (Bayer)
<b>Therapeutic Class</b>	Nonsteroidal Mineralocorticoid Receptor Antagonist
<b>Formulation</b>	Oral Tablet
<b>Dosing Regimen</b>	10 mg or 20 mg PO Daily

## Table of Contents

EXECUTIVE SUMMARY.....	3
1 Introduction.....	3
2 Background.....	4
2.1 Product Information.....	4
2.2 Regulatory History .....	5
3 Therapeutic Context and Treatment Options.....	5
3.1 Description of the Medical Condition.....	5
3.2 Description of Current Treatment Options.....	5
4 Benefit Assessment.....	8
5 Risk Assessment & Safe-Use Conditions.....	9
5.1 Hyperkalemia.....	10
6 Expected Postmarket Use .....	11
7 Risk Management Activities Proposed by the Applicant.....	11
8 Discussion of Need for a REMS.....	11
9 Conclusion & Recommendations.....	12
10 Appendices.....	12
10.1 References.....	12

## EXECUTIVE SUMMARY

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This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Kerendia (finerenone) is necessary to ensure the benefits outweigh its risks. Bayer HealthCare Pharmaceuticals Inc. (Bayer) submitted a New Drug Application (NDA) 215341 for finerenone with the proposed indication to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, nonfatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). The Division of Cardiology and Nephrology has since revised the indication to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD associated with T2D. Finerenone is associated with an increased risk for hyperkalemia. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of finerenone outweigh its risks. The increased risk for hyperkalemia is similar to other approved mineralocorticoid receptor antagonists (MRA). Finerenone is likely to be prescribed in an outpatient setting by cardiologists, nephrologists, and internists familiar with the risks of MRA therapy. Prescribers are expected to screen patients for signs and symptoms of hyperkalemia and worsening cardiovascular or renal dysfunction and optimize therapy accordingly. The safety profile of finerenone, consistent with predicted risks, and can be adequately communicated in the Warnings and Precautions section in labeling. At the time of this review, labeling was not final, therefore additional changes could occur.

## 1 Introduction

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This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Kerendia (finerenone) is necessary to ensure the benefits outweigh its risks. Bayer HealthCare Pharmaceuticals Inc. (Bayer) submitted a New Drug Application (NDA) 215341 for finerenone with the proposed indication to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, nonfatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

### 2.1 PRODUCT INFORMATION

Finerenone, a new molecular entity,<sup>a</sup> is a nonsteroidal mineralocorticoid receptor antagonist proposed to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, nonfatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with CKD and T2D. Mineralocorticoid receptor overactivation increases expression of pro-inflammatory and pro-fibrotic mediators. Mineralocorticoid receptor antagonism attenuates inflammation and fibrosis in affected cells and subsequent cardiac and renal injury.<sup>1</sup>

Finerenone is proposed to be available as 10 mg and 20 mg oral tablets. The recommended starting dose is determined using estimated glomerular filtration rate (eGFR) and serum potassium thresholds. Serum potassium  $\leq 4.8$  mEq/L is recommended for initiation of finerenone. If serum potassium is  $> 4.8$  to 5 mEq/L, finerenone initiation may be considered with additional serum potassium monitoring within the initial 4 weeks of therapy. Table 1 lists the recommended starting dose of finerenone using eGFR.

**Table 1: Recommended Starting Dosage of Finerenone**

eGFR (mL/min/1.73m <sup>2</sup> )	Starting Dose
$\geq 60$	20 mg once daily
$\geq 25$ to $< 60$	10 mg once daily
$< 25$	Not Recommended

After initiation, serum potassium and eGFR are remeasured at 4 weeks and periodically thereafter. Table 2 lists the recommended dose adjustments for continuation of finerenone therapy.

**Table 2: Continuation of Treatment and Dose Adjustment for Finerenone**

Serum potassium (mEq/L)	Finerenone dose (at 4 weeks and periodically thereafter)	
	10 mg once daily	20 mg once daily
$\leq 4.8$	Increase the dose to 20 mg once daily. If eGFR has decreased by more than 30% compared to the previous measurement, maintain 10 mg dose.	Maintain 20 mg once daily.
$> 4.8 - 5.5$	Maintain 10 mg once daily.	Maintain 20 mg once daily.
$> 5.5$	Withhold finerenone. Consider restart at 10 mg once daily when serum potassium $\leq 5$ mEq/L.	Withhold finerenone. Restart at 10 mg once daily when serum potassium $\leq 5$ mEq/L.

Duration of treatment with finerenone is expected to be long term and likely administered in an outpatient setting.<sup>b</sup> Finerenone is not currently approved in any jurisdiction.

<sup>a</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

<sup>b</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 215341 relevant to this review:

- 01/09/2015: IND 117847 submitted with Fast Track designation request.
- 02/04/2015: FDA granted Fast Track designation for the treatment of diabetic kidney disease.
- 11/09/2020: NDA 215341 received for finerenone.
- 12/09/2020: FDA granted Priority Review designation citing clinical evidence demonstrating benefit for both kidney and cardiovascular outcomes in patients with CKD and T2D.
- 02/22/2021: FDA notified the applicant that no issues warranting further discussion had been identified.

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

CKD is the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause.<sup>2</sup> T2D is the main contributor to CKD over the past three decades and the most common cause of end stage renal disease (ESRD).<sup>3</sup> A rising incidence and prevalence of ESRD, with poor outcomes and high cost<sup>4</sup>, and an ESRD population exceeding 740,000 patients<sup>5</sup> represents a significant public health burden. CKD is also associated with an increased risk of cardiovascular disease (CVD). While ESRD is the most visible outcome of CKD, patients with CKD and T2D have a greater risk for CVD mortality than developing ESRD. Additionally, patients with CKD and T2D at age 30, compared to a healthy cohort, tend to have an average life expectancy shortened by 16 years.<sup>6</sup> The need for treatment options to reduce the risk of cardiovascular and renal events in patients with CKD and T2D represent an unmet medical need.

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Non pharmacologic interventions for management of CKD and CVD in T2D include lifestyle modifications (weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, avoidance of smoking, moderation of alcohol intake, and increased physical activity). When nonpharmacological interventions do not achieve the desired results, current Kidney Disease: Improving Global Outcomes (KDIGO) and American Diabetes Association (ADA) guidelines recommend pharmacologic therapy with antidiabetic, antihypertensive, and antilipemic agents.

A sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist is recommended as part of a comprehensive glucose lowering, cardiovascular risk reduction regimen in patients with T2D. Only canagliflozin is currently FDA-approved to reduce the risk of cardiovascular and renal events in patients with T2D at this time. Cardiovascular data for SGLT2 inhibitors and GLP-1 receptor agonists used to treat T2D are listed in Table 3.

Robust evidence from clinical trials suggests targeting blood pressure (BP) reduction to at least < 140/90 mmHg in most patients with T2D to reduce cardiovascular events. Recommendations for the treatment of confirmed hypertension in patients with diabetes are outlined in Figure 1. An angiotensin-converting

enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is recommended as first-line therapy for hypertension in T2D patients with albuminuria or CVD. Other recommended antihypertensives include dihydropyridine calcium channel blockers (CCB) and thiazide-like diuretics. MRA therapy may be considered for treatment failure due to adverse effects or resistant hypertension in patients with T2D. Despite guideline recommendations, MRA therapy is limited by an increased incidence of hyperkalemia and anti-androgenic side effects. No safety issues warranting a REMS have been identified for current FDA-approved MRAs. The two FDA-approved MRAs are listed in Table 4.

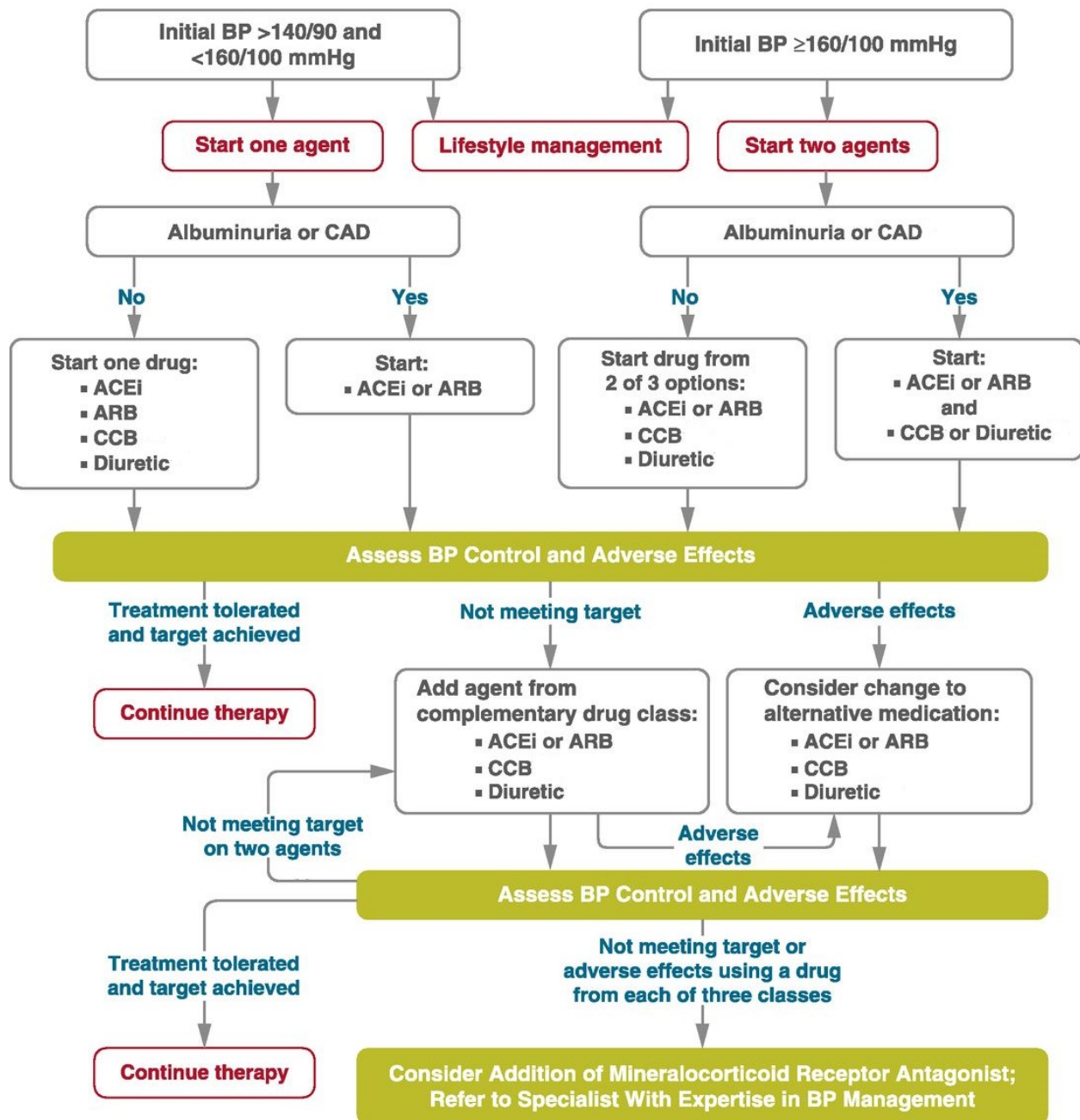
**Table 3: Cardiovascular Data for T2D Treatment with SGLT2 Inhibitors and GLP-1 Receptor Agonists**

Product Trade Name (Generic)	Outcomes Data	FDA Approval	Dosing and Administration	Important Safety and Tolerability Issues
sodium-glucose co-transporter 2 (SGLT2) inhibitor (oral)				
Invokana (canagliflozin)	Composite endpoint of CV mortality, nonfatal MI, or nonfatal stroke	Cardiovascular and Renal	100 mg or 300 mg Daily	Ketoacidosis, Necrotizing fasciitis of the perineum, genital mycotic infections
	Composite endpoint of ESRD, doubling of the serum creatinine level, or death from renal or CV causes			
Farxiga (dapagliflozin)	Composite endpoint of CV death or hospitalization for heart failure	Cardiovascular	10 mg Daily	
Jardiance (empagliflozin)	Hospitalization for heart failure, CV death, or overall death	Cardiovascular	10 mg or 25 mg Daily	
glucagon-like peptide 1 (GLP-1) receptor agonist (subcutaneous)				
Trulicity (dulaglutide)	Composite endpoint of nonfatal MI, nonfatal stroke, and death from CV or unknown causes	Cardiovascular	1.5 mg Weekly	Boxed Warning: risk of thyroid c-cell tumors
Victoza (liraglutide)	Composite endpoint of nonfatal MI, nonfatal stroke, and death from CV or any causes	Cardiovascular	1.8 mg Daily	
Ozempic (semaglutide)	Composite endpoint of nonfatal MI, nonfatal stroke, or CV death	Cardiovascular	0.5 mg or 1 mg Weekly	

**Table 4: FDA-Approved MRAs**

Product Trade Name (Generic)	Year of Approval	Indication	Dosing and Administration	Important Safety and Tolerability Issues
Aldactone (spironolactone)	1960	Treatment of hypertension	25 – 100 mg Daily or in divided doses	Hyperkalemia, Gynecomastia, Erectile Dysfunction, Dysmenorrhea
Inspra (eplerenone)	2002	Treatment of hypertension	50 mg Daily or 50 mg Twice Daily	

**Figure 1: American Diabetes Association Recommendations for the Treatment of Confirmed Hypertension in Patients with Diabetes <sup>7</sup>**





## 4 Benefit Assessment

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The efficacy of finerenone to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) and hospitalization for heart failure in adult patients with CKD and T2D was evaluated in the phase 3 FIDELIO-DKD (NCT02540993) study. The study was a randomized, double-blind, placebo controlled, parallel-group, multicenter (1024 sites in 48 countries), event-driven evaluation of finerenone in 5674 patients (finerenone group=2833, placebo group=2841)  $\geq 18$  years of age with CKD and T2D, in addition to standard of care, on the progression of kidney disease. Eligible patients had a urinary albumin-to-creatinine ratio (UACR) of 30 mg/g to  $< 300$  mg/g, an eGFR of 25 to  $< 60$  mL/min/1.73m<sup>2</sup>, and diabetic retinopathy, or they had a UACR of 300 mg/g to 5000 mg/g and an eGFR of 25 to  $< 75$  mL/min/1.73m<sup>2</sup>. All patients had a serum potassium  $\leq 4.8$  mEq/L and were treated with an ACEi or ARB. The study design included a run-in period to optimize ACEi or ARB therapy, with subsequent randomization to two treatment groups. The starting dose of study drug depended on the eGFR level: 10 mg once daily if eGFR was 25 to  $< 60$  mL/min/1.73m<sup>2</sup>, and 20 mg once daily if eGFR was  $\geq 60$  mL/min/1.73m<sup>2</sup>. After 4 weeks, escalation to the target dose of 20 mg once daily was permitted if serum potassium was  $\leq 4.8$  mEq/L and if eGFR had not decreased by  $> 30\%$  compared to the prior visit. The study drug dose was titrated up or down according to the study titration rules.

Baseline demographics and clinical characteristics were balanced between the two treatment groups and generally representative of a patient population with CKD and T2D. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of eGFR  $\geq 40\%$  from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. During a median follow up of 2.6 years, a primary outcome event occurred in 504 patients (17.8%) in the finerenone group and 600 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93;  $p = 0.001$ ). A key secondary outcome event occurred in 367 patients (13%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99;  $p = 0.03$ ). A sustained decrease of eGFR  $\geq 40\%$  from baseline was the main contributing component to the relative risk reduction of the primary composite outcome. With the exception of nonfatal stroke, all components contributed to the relative risk reduction of the secondary composite outcomes. The efficacy outcomes are summarized as components of the composite outcomes in Table 5.

**Table 5: Efficacy Outcomes Including Components of the Composite Outcomes**

Outcome	Finerenone (N = 2833)	Placebo (N = 2841)	Hazard Ratio (95% CI)	P Value
	n (%) patients			
Primary Composite Outcome	504 (17.8)	600 (21.1)	0.82 (0.73-0.93)	0.001
Kidney Failure	208 (7.3)	235 (8.3)	0.87 (0.72-1.05)	-
ESRD	119 (4.2)	139 (4.9)	0.86 (0.67-1.10)	-
Sustained Decrease in eGFRto < 15 mL/min/1.73m <sup>2</sup>	167 (5.9)	199 (7)	0.82 (0.67-1.01)	-
Sustained Decrease of eGFR ≥ 40% from Baseline	479 (16.9)	577 (20.3)	0.81 (0.72-0.92)	-
Death from Renal Causes	2 (< 0.1)	2 (< 0.1)	-	-
Key Secondary Composite Outcome	372 (13)	420 (14.8)	0.86 (0.75-0.99)	0.03
Death from Cardiovascular Causes	128 (4.5)	150 (5.3)	0.86 (0.68-1.08)	-
Nonfatal Myocardial Infarction	70 (2.5)	87 (3.1)	0.80 (0.58-1.09)	-
Nonfatal Stroke	90 (3.2)	87 (3.1)	1.03 (0.76-1.38)	-
Hospitalization for Heart Failure	139 (4.9)	162 (5.7)	0.86 (0.68-1.08)	-

Source: Adapted from applicant's original submission on November 9, 2020; Tables 2-15 and 2-17 in Module 2.7.3

The Applicant concluded the treatment benefit of finerenone for the primary and key secondary endpoints was consistent across all components of the composite endpoints except for nonfatal stroke. The clinical review team modified the finerenone indication during the review to align with specific primary and secondary outcomes from the FIDELIO-DKD study. The modified indication for finerenone is to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with T2D (b) (4). At the time of this review, labeling is still under negotiation. With acknowledgment of the small number of deaths from renal causes and the similar incidences of nonfatal stroke between the two treatment groups, the clinical reviewer concluded substantial evidence of effectiveness supported the benefit of finerenone in reducing the risk of kidney failure, sustained decrease in eGFR ≥ 40% from baseline, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD and T2D. This determination relied on the favorable outcomes observed throughout the duration of the FIDELIO-DKD study.

## 5 Risk Assessment & Safe-Use Conditions

The primary safety analysis of finerenone, referred to as the safety analysis set or SAF population, relies on data from the FIDELIO-DKD study. The SAF population represents 2827 patients with CKD and T2D who received at least one dose of either 10 mg or 20 mg of finerenone. Overall, the frequency of adverse events was similar between the finerenone group (87.3%) and placebo (87.5%). Three key adverse events observed more frequently, and with an incidence of ≥ 1% in the finerenone group were hyperkalemia, hypotension, and hyponatremia. Common and select adverse events related to the mechanism of action and therapeutic drug class of finerenone, and a CKD and T2D patient cohort are summarized in Table 6.

**Table 6: Summary of Adverse Events During Treatment – Safety Analysis Set**

Adverse Event (AE) Category	Finerenone (N = 2827)	Placebo (N = 2831)
	n (%) patients	
SAE with Outcome of Death	31 (1.1)	51 (1.8)
Hyperkalemia	516 (18.3)	255 (9)
SAE of Acute Kidney Injury	56 (2)	51 (1.8)
Hypotension	126 (4.5)	87 (3.1)
Hyponatremia	40 (1.4)	19 (0.7)

Source: FDA Review Team Analysis in ongoing Finerenone Unireview (Accessed on 5/27/2021)

Serious treatment emergent adverse events (TEAEs) leading to treatment discontinuation were balanced between the finerenone group (2.7%) and placebo (2.8%). TEAEs of gynecomastia were uncommon in both groups (< 0.5%). A greater incidence of SAE with a fatal outcome occurred in the placebo group (1.8%) as compared to the finerenone group (1.1%). The clinical reviewer focused on the following TEAEs in the safety analysis set: hypotension, hyponatremia, acute kidney injury (AKI), and hyperkalemia.

Mild to moderate hypotension occurred more frequently in patients treated with finerenone. The Applicant proposed inclusion of hypotension as an adverse event in the label. The clinical reviewer determined the events were mostly non-serious, rarely led to treatment discontinuation, and will be identified as an adverse event in the label.

Mild hyponatremia occurred more frequently in patients treated with finerenone. Hyponatremia led to treatment discontinuation for one patient in the finerenone group compared to none in the placebo group. The Applicant proposed inclusion of hypotension as an adverse event in the label. The clinical reviewer determined hyponatremia will be identified as an adverse event in the label citing the mechanism of action of finerenone.

The risk of AKI with finerenone was evaluated citing diuretic effects of MRAs and the potential to cause volume depletion. The incidence of serious AKI events was similar between the finerenone group (2%) and placebo (1.8%). The dose of study drug was not changed for the majority of patients who had an AKI treatment emergent adverse event. The incidence of study drug withdrawal was low in both the finerenone group (0.2%) and placebo (0.3%). Changes in serum creatinine and eGFR generally occurred within one month of initiating finerenone therapy and then stabilized regardless of baseline kidney function. The clinical reviewer recommended a statement in the Adverse Events section of the label for further evaluation of patients with changes not fitting this pattern to exclude the possibility of AKI.

## 5.1 HYPERKALEMIA

The risk of hyperkalemia with finerenone is consistent with characteristics of the drug class and mechanism of action. Hyperkalemia occurred more frequently in the finerenone group (18.3% [516/2827]) compared to placebo (9% [255/2831]) and was mild or moderate in intensity. Hyperkalemia was the most frequent TEAE resulting in permanent discontinuation of study drug. Discontinuation due to hyperkalemia occurred more frequently in the finerenone group (1.8% [51/2827]) compared to placebo (0.7% [19/2831]). Two patients in the finerenone group had a serious adverse event of

hyperkalemia and died during the study. The clinical reviewer determined finerenone was not a causative factor for hyperkalemia or death after review of the patient narratives. The dose initiation protocol and maintenance dosing regimen proposed by the applicant were justified relying on serum potassium thresholds associated with the smallest relative risk for hyperkalemia. The Applicant proposed precautionary language for an increased incidence of hyperkalemia in the Warnings and Precautions section of the label. The clinical reviewer agrees with including hyperkalemia in Warnings and Precautions and that labeling is sufficient to address this risk.

The clinical reviewer concluded the safety profile of finerenone is consistent with predicted risks of MRA therapy and the overall benefit-risk profile appears acceptable.

## 6 Expected Postmarket Use

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Finerenone is likely to be prescribed in an outpatient setting by cardiologists, nephrologists, and internists familiar with the risks of MRA therapy. Prescribers are expected to screen patients for signs and symptoms of hyperkalemia and worsening cardiovascular or renal dysfunction and optimize therapy accordingly. Currently available MRA therapy is used off-label for anti-androgenic effects. Lower affinity for the androgen receptor likely limits off-label use of finerenone observed with existing MRA therapy.

## 7 Risk Management Activities Proposed by the Applicant

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The applicant did not propose any risk management activities for finerenone beyond routine pharmacovigilance and labeling.

## 8 Discussion of Need for a REMS

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The clinical reviewer recommends approval of finerenone citing the favorable outcomes observed throughout the duration of the phase 3 FIDELIO-DKD study, the seriousness of CKD and T2D, and an adequately favorable benefit-risk profile.

CKD is the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause. T2D is the main contributor to CKD and the most common cause of ESRD. Patients with CKD and T2D are also at increased risk of CVD. The elevated risk for renal and cardiovascular disease result in significant morbidity and mortality in patients with CKD and T2D.

The FIDELIO-DKD study evaluated the efficacy of finerenone to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) and hospitalization for heart failure in adult patients with CKD and T2D. The study demonstrated a statistically significant relative risk reduction of the primary composite outcome (kidney failure, a sustained decrease of eGFR  $\geq$  40% from baseline, or death from renal causes) and secondary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) in the finerenone group compared to placebo.

The serious risk associated with finerenone is hyperkalemia. The risk for hyperkalemia, dosing recommendations, and consideration for initiating appropriate medical treatment for elevated serum potassium levels will be found in the Warnings and Precautions section of the label.

Relying on the data available and prescribers' likely familiarity with the risks associated with finerenone, the risk of hyperkalemia does not pose safety concerns that require a REMS to ensure the benefit outweigh the risks. DRM is not recommending a REMS for the management of the risks of finerenone therapy.

## 9 Conclusion & Recommendations

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Relying on the data available, a REMS is not necessary to ensure the benefits of finerenone outweigh the risk for hyperkalemia. The risk for hyperkalemia is communicated in labeling using the Warnings and Precautions section of the label. The safety concerns associated with finerenone use and other MRAs are similar. In general, healthcare providers who treat patients with CKD and T2D are familiar with monitoring and treating the risk of hyperkalemia and worsening cardiovascular or renal dysfunction. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>1</sup> Kolkhof P, Barfacker L. 30 Years of the Mineralocorticoid Receptor: Mineralocorticoid receptor antagonists: 60 years of research and development. *J Endocrinol.* 2017;234(1):T125-T140.

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<sup>4</sup> Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; 108:2154.

<sup>5</sup> United States Renal Data System. 2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2019.

<sup>6</sup> Wen CP, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney International.* 2017;92(2):388-396.

<sup>7</sup> American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl.1):S125–S150.

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