CAPTIVATE
The Chronic kidney disease Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect

MRA Domain Specific Appendix (DSA)

Guidance for initiation and management of finerenone

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1 INTRODUCTION

This document provides guidance around the initiation and dosing of finerenone, and management of treatment-related adverse events during the conduct of the Finerenone Domain Specific Appendix (DSA) of the CAPTIVATE trial. Finerenone is a selective mineralocorticoid receptor antagonist that prevents the binding of aldosterone, a key hormone in the renin-angiotensin-aldosterone-system (RAAS), which is involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease. The trial aims to determine whether finerenone reduces albuminuria and the rate of estimated glomerular filtration rate (eGFR) decline compared to placebo in patients with chronic kidney disease (CKD) receiving standard of care. This document provides broad recommendations and should not replace clinical decisions made by treating physicians.

For further guidance please contact your study nurse, site principal investigator and/or the CAPTIVATE study physician on captivate@georgeinsitute.org.au

2 INITIATION OF FINERENONE

The initiation dose of finerenone is dependent on eGFR (Table 1). The eligibility criteria for the MRA domain at the time of screening includes:

- eGFR >25mL/min/1.73m^2
- Serum potassium (K+) <5.0mmol/L

If the eGFR at the time of randomisation falls below <20mL/min/1.73m^2, finerenone commencement is not recommended. Once finerenone has been commenced and established at a stable dose of either 10mg daily or 20mg daily, ongoing treatment is permitted at any level of kidney function. Finerenone should be suspended if serum potassium >5.5mmol/L at any point in the study.

Table 1. Recommended starting dose and dose adjustment of finerenone

Baseline eGFR (mL/min/1.73m^2)	**Starting Dose**	**Dose at 4 weeks and thereafter Dependent on serum potassium levels (K+, mmol/L)**		
	K+ < 5.0	**K+ < 5.0**	**K+ 5.0-5.5**	**K+ >5.5**
≥ 60	20mg once daily	20mg once daily	20mg once daily	Suspend Restart at 10 mg once daily if serum potassium <5.0 mmol/L
25-59	10mg once daily	Increase the dose to 20mg once daily if eGFR decrease is ≤ 30% lower than the eGFR value at the previous visit	10mg once daily	Suspend Restart at 10 mg once daily if serum potassium <5.0 mmol/L

3 CONTINUATION OF FINERENONE

3.1 Ongoing dosage

The ongoing dose is dependent on eGFR and serum potassium. Re-measure eGFR and serum potassium 4 weeks after initiation or re-commencement of finerenone to monitor for hyperkalaemia and to guide ongoing dose. Refer to Figure 1 to determine ongoing finerenone dose and adjustments as appropriate. If serum potassium is >5.5mmol/L at any point, refer to 5.1 for management recommendations.

4 STANDARD OF CARE

The current international standard of care guidelines for individuals with CKD and albuminuria include maximal RAS blockade with an angiotensin 2 receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor and sodium glucose co-transporter 2 (SGLT2) inhibitor therapy unless unavailable or contraindicated. Participants should be established on both agents at a stable dose for at least 4 weeks prior to enrolment.

Both RAS and SGLT2 inhibitors can lower blood pressure, therefore, consider the participant's blood pressure at randomisation and risk of symptomatic hypotension if either of these agents are altered. RAS blockade can increase serum potassium. There is evidence that concurrent SGLT2i therapy can lower serum potassium in those receiving finerenone (Rossing et al. KI Reports 2022). Therefore, consider repeating serum potassium levels if either of these drugs are added, omitted, or adjusted during the study.

5 SIDE EFFECTS

You should be alert to the following events in all trial participants. The following information is for guidance only. The management of acute severe side effects is beyond the scope of this document. Please refer to local guidelines and the treating physician.

Table 3. Side effects of finerenone

Frequency	Side Effect
Very common (≥10%)	Hyperkalaemia
Common (≥1%)	Hypotension, decreased glomerular filtration rate, hyponatraemia, hyperuricemia

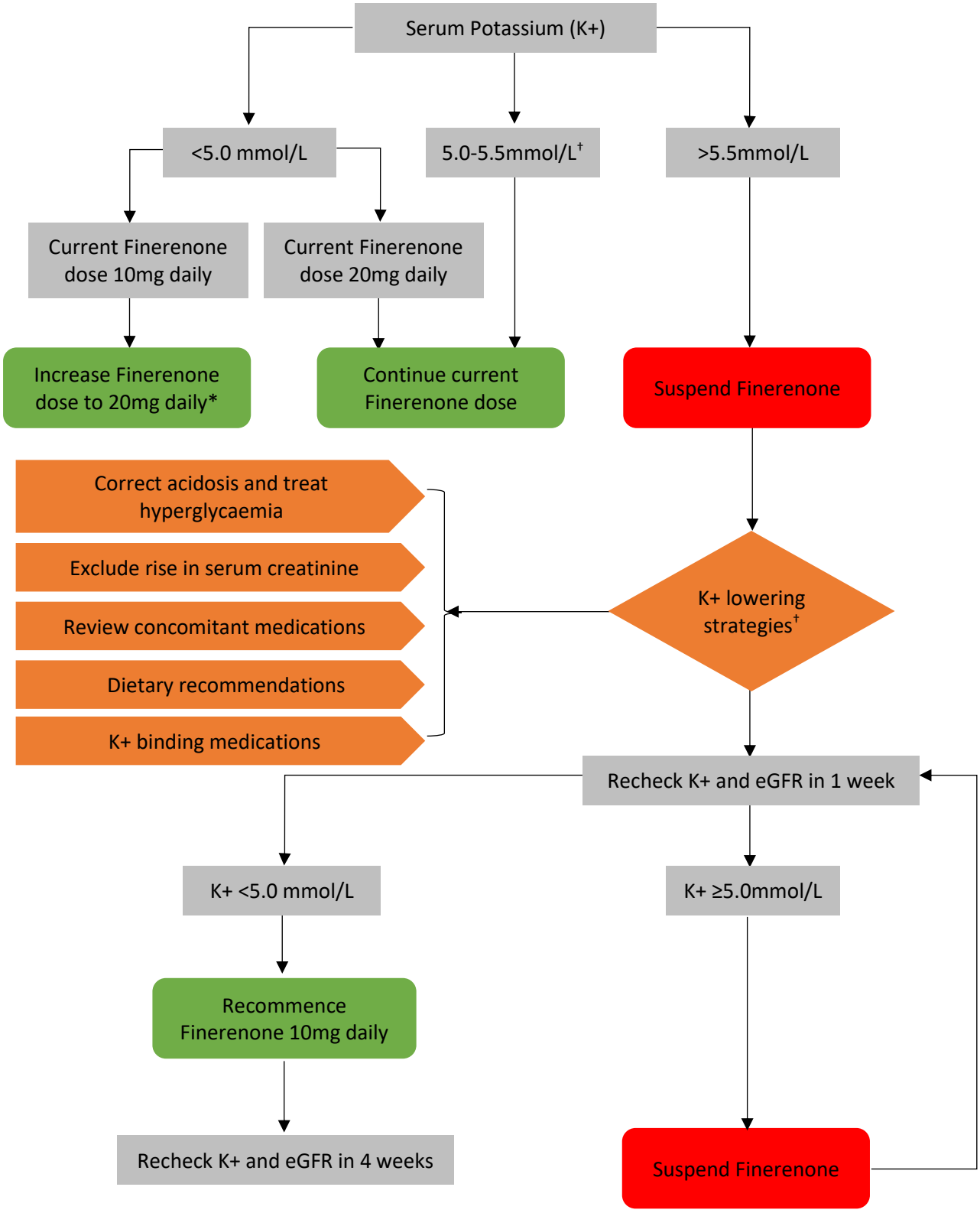
5.1 Hyperkalaemia

5.1.1 Considerations for evaluating and treating hyperkalaemia

For the MRA domain, hyperkalaemia is defined as an elevated serum potassium of >5.5mmol/L. Severe hyperkalaemia is defined as a serum potassium of ≥6.0mmol/L.

Define hyperkalaemia
• Acute hyperkalaemia: Serum potassium above the upper limit of normal with no known underlying chronic cause. • Chronic hyperkalaemia: Serum potassium above the upper limit of normal on repetitive measurements over 3 months likely secondary to a chronic cause (e.g. chronic kidney disease, heart failure, regular medications/supplements). • Pseudo-hyperkalaemia: Falsely elevated serum potassium (e.g. difficult blood draw, mechanical trauma, prolonged tourniquet use, elevated white blood cell or platelet counts, blood clotting).
Review potential precipitants for acute hyperkalaemia
• Medications such as potassium supplements and potassium-sparing diuretics (Table 4) • Decompensated heart failure • Acute kidney injury • Acidosis
Treat clinically significant hyperkalaemia (K+ >5.5mmol/L)
• Confirm result on repeat specimen if pseudo-hyperkalaemia is suspected. • Reduce/suspend finerenone dose as per algorithm (Figure 1). • Review ECG if K+ ≥6.0mmol/L. • Check serum creatinine (eGFR). • Correct acidosis with sodium bicarbonate. • Cease potassium supplements. • Consider reducing/ceasing other medications associated with hyperkalaemia if appropriate. • Implement dietary considerations (5.1.2). • Consider potassium lowering agents (Table 5). • The potassium should be repeated at an appropriate interval to assess potassium stability.
When to refer
• The decision to commence potassium binding agents should be made by the treating physician. • The management of severe acute hyperkalaemia (K+ ≥6.0mmol/L) is beyond the scope of this guidance document.

Figure 1. Approach to finerenone dosing based on serum potassium and considerations for hyperkalaemia management



**if eGFR decrease is ≤ 30% lower than the eGFR value at the previous visit*

† *Consider implementing potassium (K+) lowering strategies if serum potassium ≥5.0mmol/L regardless of whether finerenone is continued or ceased*

Table 4. Examples of medications associated with hyperkalaemia*

Category	Examples
Potassium supplements	Slow K, Span K, Chlorvescent
Potassium-sparing diuretics	Amiloride
Agents targeting the RAAS	ACE inhibitors ARBs Spironolactone# Eplerenone# Angiotensin receptor-neprilysin inhibitors
Other	NSAIDs and COX2 antagonists$ Beta blockers Trimethoprim Heparin

**Availability and practice patterns may differ across different countries and regions*
 # Participants in the MRA DSA of the CAPTIVATE study should not be receiving these medications
$ The Australian Medicines Handbook advises that the use of NSAIDs or COX2 antagonists should be reviewed for concomitant use with an ARB especially in the context of deteriorating renal function.

Table 5. Potassium lowering medications

Drug	Mechanism of Action	Onset	Dose	Adverse Effects*
Polystyrene sulfonate Resins	Sodium or calcium ions are exchanged for potassium ions in the GIT, which are then excreted faecally.	Several hours	Oral: Commence at 15g daily, up to maximum four times daily Rectal: 30g once daily	GIT: Constipation, faecal impaction, diarrhoea, nausea, vomiting, anorexia Electrolyte disturbances: Hypokalaemia, hypomagnesaemia, hypernatraemia, hypo/hypercalcaemia Rare/severe: Ischaemic colitis, GIT obstruction, ulceration, performation or necrosis
Patiromer	Cation exchange polymer that binds potassium ions in the GIT lumen which are then excreted faecally.	4-7 hours	Commence at 8.4g once daily, up to maximum 25.2g daily	GIT: Constipation, diarrhoea, pain, flatulence, nausea, vomiting Electrolyte disturbances: Hypokalaemia, hypomagnesaemia
Sodium zirconium cyclosilicate	Binds potassium ions in exchange for hydrogen and sodium cations in	4 hours	Commence at 10g up to a maximum three times daily for	Oedema Hypokalaemia

	the GIT, which are then excreted faecally.		48 hours, then maintenance of maximum 10g once daily.	

The dose and duration of potassium exchange resin administration should be as low and as short as possible. Cease when no longer required. Patiromer and zirconium are not currently available in India or New Zealand.
** Patiromer and sodium zirconium cyclosilicate have not been studied in patients with severe constipation, a history of bowel obstruction, major gastrointestinal surgery or post-operative bowel motility disorders.*
Abbreviations: GIT, gastrointestinal tract

5.1.2 Dietary approaches to hyperkalaemia

The extreme restriction of dietary potassium is not recommended by international guidelines as data suggest it does not correlate well with serum potassium (K+). Please apply the following recommendations to manage hyperkalaemia:

- Reduce processed meat
- Limit ultra-processed foods as these often contain K+ additives
- Double boil foods and discard cooking water to reduce K+ content
- Treat constipation to enhance gastrointestinal K+ excretion such as maintaining a high fibre diet and adequate fluid intake
- Refer to a dietitian for individualised nutrition care for individuals with advanced CKD

5.2 Hypotension

5.2.1 Considerations for evaluating and treating hypotension

Evaluate the patient's clinical status
• Is the patient symptomatic (e.g. dizziness, weakness)? • Look for a deteriorating clinical condition (e.g. heart failure, sepsis). • Evaluate fluid status.
Management of hypotension
• Correct volume loss. • Treat the underlying precipitating cause (e.g. cardiac event, infection). • Review and consider ceasing other blood pressure lowering agents including other diuretics if possible. • Consider reducing/suspending/ceasing finerenone.
Medication considerations
• Continue standard of care (e.g. RAS inhibitor, SGLT2 inhibitor), keeping in mind these can cause hypotension. • Most non-potassium-sparing diuretics (e.g. frusemide) lower serum potassium, therefore the cessation of these agents may induce hyperkalaemia. • The concomitant use of alpha-1-blockers (e.g. prazosin) increases the potential for hypotension and/or postural hypotension. • Co-administration of tricyclic anti-depressants, neuroleptics and baclofen may increase the antihypertensive effects of finerenone.
When to refer

• If a patient has signs of a deteriorating clinical condition, please refer to their treating physician. • The management of severe hypotension (BP < 90/60mmHg) or symptomatic hypotension is beyond the scope of this guidance document.

5.3 eGFR decline (rise in serum creatinine)

5.3.1 Definition of acute kidney injury

As per the KDIGO guidelines, an acute kidney injury (AKI) is defined as any of the following:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/h for 6 hours

5.3.2 Approach to a rise in serum creatinine

A rise in serum creatinine can be defined as acute or chronic and can be expected or unexpected. Detailed assessment is beyond the scope of this document, however some considerations are outlined.

Expected rise in creatinine
• An expected result of finerenone is a single rise in creatinine (or reduction in eGFR) of ≤30% within the first 4 weeks of drug commencement due to renal haemodynamic changes. • This rise in creatinine is reversible within 4 weeks of drug discontinuation.
Unexpected rise in creatinine
• A rise in creatinine by >30% is not typically seen following commencement of finerenone. If this occurs, consider rechecking the creatinine at an appropriate time interval considering the clinical situation and the degree of rise. • A progressive rise in creatinine (i.e. decline in eGFR) is not an expected effect of finerenone and this should prompt further evaluation for other causes of AKI.
Evaluate the patient's clinical status
• Look for deteriorating clinical condition • Assess fluid status looking for signs of dehydration, hypotension, or reduced urine output.
Assess for precipitants for AKI
• Acute illness or condition (e.g. cardiac event, sepsis • Dehydration, volume loss, hypotension • Initiation or change in medications with nephrotoxic potential (e.g. NSAIDs, COX2 inhibitors, aminoglycosides, amphotericin B, iodinated contrast, cyclosporin, tacrolimus) • Urological obstruction
Management of AKI
• In the presence of dehydration correct volume loss. • In the presence of hypotension consider reducing other blood pressure lowering agents and/or diuretics (apart from standard of care). • If urological obstruction is suspected, arrange imaging of the renal tract.

• Consider reducing/suspending/ceasing finerenone.
When to refer
• If a patient has signs of a deteriorating clinical condition, please refer to their treating physician. • Urological obstruction may warrant specialist urological opinion and management. • The management of a progressive rise in creatinine is beyond the scope of this guidance document.

6 RESTARTING FINERENONE

Should the conditions that required study medication discontinuation no longer exist, finerenone or should be re-started if it is clinically appropriate to do so. Refer to Figure 1 for guidance around recommencement in the case of hyperkalaemia.

7 CEASING FINERENONE

Finerenone should be ceased if:

- Serum K+ >5.5mmol/L on 2 occasions during the study period
- If the drug has been withheld on 2 occasions due to hyperkalaemia

Please refer to the MRA Domain Specific Appendix for additional protocol specified requirements for drug discontinuation. The patient will continue to be followed up in the trial to allow intention to treat analyses (unless they expressly withdraw consent).

8 CONTRACEPTION

Effective contraceptive methods are to be used throughout the study period.
Contraceptives[a] allowed during the study are outlined below.

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

[a]*Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.*

[b]*Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.*

[c]*Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.*

[d]*Considered effective, but not highly effective - failure rate of ≥ 1% per year.*

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

9 REFERENCES AND ADDITIONAL RESOURCES

Please contact the CAPTIVATE team for any further questions on the content in this document or the local site contact to contact.

- Australian Therapeutic Goods Administration Product Information for Kerendia available at https://www.tga.gov.au/resources/auspar/auspar-finerenone
- Rossing P, Filippatos G, Agarwal R, Anker SD, Pitt B, Ruilope LM, Chan JCN, Kooy A, McCafferty K, Schernthaner G, Wanner C, Joseph A, Scheerer MF, Scott C, Bakris GL; FIDELIO-DKD Investigators. Finerenone in Predominantly Advanced CKD and Type 2 Diabetes With or Without Sodium-Glucose Cotransporter-2 Inhibitor Therapy. Kidney Int Rep. 2021 Oct 14;7(1):36-45. doi: 10.1016/j.ekir.2021.10.008. PMID: 35005312; PMCID: PMC8720648.
- The International Society of Nephrology Optimization of RAASi Therapy Toolkit available at https://www.theisn.org/initiatives/raasi-toolkit/#Challenges
- The Therapeutic Guidelines on the treatment of hyperkalaemia available at https://tgldcdp.tg.org.au.acs.hcn.com.au/viewTopic?topicfile=electrolyte-abnormalities&guidelineName=Other#toc_d1e1118
- Up to Date recommendations on the treatment and prevention of hyperkalaemia available at https://www.uptodate.com/contents/treatment-and-prevention-of-hyperkalemia-in-adults