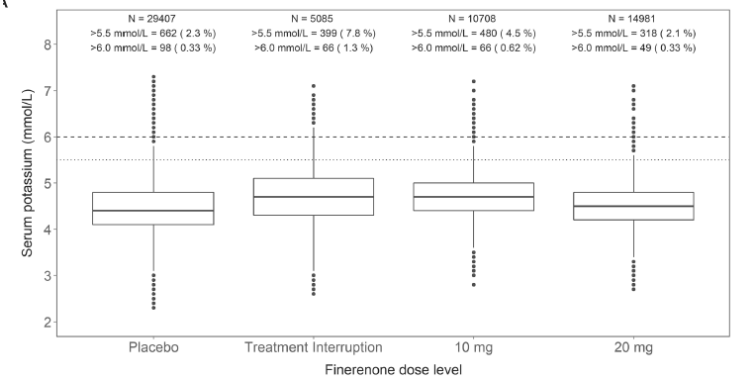
Finerenon + CYP3A4-remmers | M 8409

Onderbouwend	Stof	Effect	Code
Wendl T. CPT Pharmacometrics Syst Pharmacol 2022;11:199-211. PBPK: Physiologically-based pharmacokinetic model *observed data from dedicated clinical interaction studies	finerenon + erytromycine, verapamil finerenon + itraconazol, claritromycine	PBPK model finerenone - erythromycin: simulated ratio AUC 3.46 and Cmax 2.00 vs observed* 3.48 resp. 1.88 - verapamil simulated ratio AUC 2.91 and Cmax 1.86 vs observed 2.70 resp. 2.22. The model was applied to predict clinically untested DDI studies with CYP3A4 modulators. *predicted ratio AUC resp.* Cmax - itraconazole 6.31 2.37 - clarithromycin 5.28 2.25	1-2A
Heinig R. Eur J Drug Metab Pharmacokinet 2018;43:715-727.	finerenon + erytromycine, verapamil	*ratio AUC finerenon+ inhibitor/finerenon alone* erythromycin 3.48 verapamil 2.70 Methods: finerenone (1.25-10 mg orally or 0.25-1.0 mg i.v.), 4 crossover studies with healthy male volunteers. Absolute bioavailability was assessed in volunteers receiving finerenone orally and by i.v. infusion (n = 15); the effects of erythromycin (n = 15), verapamil (n = 13) on finerenone PK were investigated. Finerenone was also incubated with cryopreserved human hepatocytes in vitro in the presence of these 3 inhibitors. Conclusion: finerenone is predominantly metabolized by CYP3A4 in the gut wall and liver. The absolute bioavailability was 43.5% due to first-pass metabolism metabolic clearance due to CYP2C8 involvement. The contribution ratio of CYP3A4 to the metabolic clearance derived from these values was 0.88-0.89 and was consistent with estimations based on in vitro data, with the remaining metabolic clearance due to CYP2C8 involvement. Inhibition of CYP2C8 has no relevant effect on finerenone in vivo.	3A
Spc/EPAR Kerendia fysiologisch-gebaseerde farmacokinetische (PBPK-) simulaties	finerenon + erytromycine finerenon + itraconazol, claritromycine finerenon + verapamil	↑AUC finerenon 3.5x en Cmax 1.9x. Regime: finerenon 1.25 mg, erytromycine 500 mg 3dd (‘matige 3A4-remmer’), 15 vrijwilligers → getallen uit Heinig 2018 ↑AUC finerenon 6x Regime: PBPK-simulatie met itraconazol of claritromycine (‘sterke 3A4-remmers’) ↑AUC finerenon 2.7x en Cmax 2.2x Regime: finerenon 5 mg, verapamil tablet mga 240 mg 1dd (‘matige 3A4-remmer’), 13 vrijwilligers → getallen uit Heinig 2018	1A
Kerendia usa https://www.kerendia-us.com/	finerenon + itraconazol, erytromycine	Drug Interaction Studies: Clinical Studies and Model-Informed Approaches - itraconazole (strong CYP3A4 inhibitor): ↑ finerenone AUC by >400%. - erythromycin (moderate CYP3A4 inhibitor): ↑ finerenone AUC by 248% and Cmax by 88%.	1A

Overig	Stof	Effect
Spc Kerendia	finerenon + CYP3A4-remmers	substraat voor CYP3A4 (hoofdroute, 90%) en 2C8 (10%). -krachtige CYP3A4-remmers: combi gecontra-indiceerd.

		-matige of zwakke CYP3A4-remmers: serumkalium kan stijgen, monitor serumkalium, met name tijdens het instellen of wijzigingen aan de dosering van finerenon of de CYP3A4-remmer. Rubriek Overdosering: de meest waarschijnlijke manifestatie van overdosering is naar verwachting hyperkaliëmie.
Yu J. Clin Ther 2022;44:1536-44.	finerenon + itraconazol	review: ↑ AUC 6.33x en Cmax 2.37x obv PBPK model met finerenon 10 mg 1-malig en itraconazol 200 mg 2dd (data uit product label Kerendia) Methods: DDI data for small molecular drugs approved by the FDA in 2021 were analyzed using the University of Washington Drug Interaction Database. The mechanism(s) and clinical magnitude of these interactions were characterized based on information available in the new drug application reviews. Clinical studies and simulation results with mean AUC ratios (AUCRs) ≥5 for inhibition DDIs (ie, strong interactions) were then fully analyzed. Conclusion: finerenone is a sensitive substrate of CYP3A.
Goulooze SC. Clin Pharmacokinet 2022;61:451-62.	finerenon	Analyse van serumkaliumspiegels van patienten uit FIDELIO-DKD studies, waarbij het lijkt of het effect op kalium minder groot is 20 mg dan bij 10 mg. The analysis of serum potassium values and finerenone exposure or dose revealed an apparent inverse relationship not in line with a naive “traditional” assumption, where the highest hyperkalemia risk would be expected at the highest dose level (Fig. 1). The model-based analysis can explain this phenomenon. 

Opmerkingen
Werkgroep Interacties & MFB’s 18-11-24: de uitgangspunten van de bestaande MFB Kalium zijn ook hier van toepassing voor verfijning.

Idem 27-6-24: actie Ja, tevens verapamil koppelen. Advies: vermijd combinatie, als dit niet kan controleer K extra.

Stockley online feb 2024: severe, avoid, theoretical (Ketoconazole is predicted to increase the exposure to finerenone.)

Risicofactoren	
Mitigerende factoren	

	Interactie	**Actie**	**Datum**
Beslissing WG IA	Ja	Ja	27 juni 2024