Eplerenon + CYP3A4-remmers M 692

Onderbouwend	Stof	Effect	Code
SPC Inspra & Inspra FDA label FDA label wat meer info omtrent Cmax en Regime.	eplerenon + ketoconazol, eplerenon + erytro, fluco, verapamil	↑ AUC eplerenon 5.4x en Cmax 1.7x Regime (vlg Stockley): ketoconazole 200 mg 2dd 7 dagen, 18 gezonde vrijwilligers. ↑ AUC 2-2.9x en Cmax 1.4-1.6x door erytromycine, verapamil, fluconazol Regime (FDA): erytromycine 500 mg 2dd, verapamil 240 mg 1dd, fluconazol 200 mg 1dd.	1A

Overig	Stof	Effect
SPC Inspra & Inspra FDA label	eplerenon + remmers	-sterke CYP3A4-remmers (itraconazol, ketoconazol, ritonavir, claritromycine): combinatie is gecontraïndiceerd. -zwakke tot matige remmers CYP3A4 (zoals erytromycine, fluconazol, verapamil): dosering eplerenon max. 25 mg 1dd bij combinatie. FDA: verlaag startdosis naar 25 mg 1dd. Er zijn geen gevallen van overdosering bekend. Hyperkaliëmie ligt voor de hand. K-spiegel wordt standaard al periodiek gecontroleerd.
Hirai T. J Hypertens 2023;41:580-6. MRAs: mineralocorticoid receptor antagonisten, in deze studie eplerenon en esaxerenone (niet in de handel in Ned.) Patients were excluded if they had a baseline serum potassium level >5.5 meq/l, defined as Grade 2 or higher hyperkalemia according to Common Terminology Criteria for Adverse Events version 5.0.	MRAs + claritromycine eplerenon + claritromycine (esaxerenone + claritromycine)	after propensity score matching (each 9 patients): - MRA plus clarithromycin: ↑serum potassium level 4.3 →4.9 meq/l - MRA alone: ↑serum potassium level 4.3 → 4.6 meq/l Overall (MRAs combined), there was no significant difference in ΔK between groups, MRA plus clarithromycin vs MRA alone 0.5 vs 0.3 meq/l. No significant effect of clarithromycin on ΔK vs eplerenone alone: 0.4 vs 0.8 meq/l [P = 0.5745]. A positive correlation was found between ΔK and age in patients with MRA plus clarithromycin vs eplerenone alone: 0.4 vs 0.8 meq/l [P = 0.5745]. The effect of clarithromycine on ΔK was significantly higher for esaxerenone plus clarithro vs esaxerenone alone: 0.6 vs 0.1 meq/l [P = 0.0495]. Methods: retrospective observational study with hypertensive patients with MRA plus clarithromycin* (n=9) or MRA alone (n=224) with a propensity score matching (1:1); * daily dose 200mg 2dd (n=6) of 400 mg 2dd (n=3). Conclusion: the interaction between MRAs and clarithromycin was evident, particularly in esaxerenone. Serum potassium levels should be closely monitored in older patients.
Cordova E. Int J STD AIDS 2021;32:771-3. Geen pdf, alleen abstract PubMed	eplerenon + ritonavir	abstract casus: a 48-year-old white HIV-1 positive man presented an acute myocardial infarction. The patient was on ART for the last ten years with fosamprenavir/rtv and emtricitabine/tenofovir. Eplerenone 25 mg/day was also initiated due to a left ventricular dysfunction. A week after discharge a routine laboratory examination revealed severe hyperkalaemia. Both eplerenone and ARVs were interrupted. Despite daily treatment for hyperkalaemia, serum potassium levels normalized after 2 weeks. Werkgroep Interacties & MFB's 27-6-24: niet onderbouwend, uitgangswaarde kalium niet bekend, mogelijk bijwerking eplerenon.

Kato J. Eur J Clin Pharmacol 2009;65:323-4. Letter to editor.	eplerenon + voriconazol en nifedipine	Omschrijving deels vlg Stockley online: 'a case report describes the development of hypotension (130-146→76 mmHg en 70-88→48 mmHg na 1 dag voriconazol) when i.v. voriconazole was started in a patient stable taking eplerenone 50 mg daily and nifedipine 40 mg daily. A complete resolution was achieved by stopping the eplerenone and halving nifedipine daily dose. However, it is unclear to what extent the eplerenone contributed to the hypotensive effects seen, as nifedipine concentrations can, in theory, also be increased by voriconazole.' Werkgroep Interacties & MFB's 27-6-24: niet onderbouwend, 'driehoeksrelatie' door gebruik nifedipine.
Cook CS. Xenobiotica 2004;34:215-28. doi: 10.1080/00498250310001649341.	eplerenon + erytromycine, fluconazol, ketoconazol, verapamil	Prediction of in vivo drug interactions with eplerenone in man from in vitro metabolic inhibition data (human liver microsomes). The Ki values for the inhibition of EP 6beta-hydroxylation by erythromycin, fluconazole, ketoconazole, and verapamil were 9.50, 59.0, 0.160, and 13.3 microM, respectively. Among the three methods, inhibition factors (Rb) calculated using the Ki and estimated liver Cmax values of the unbound drug were best correlated with the in vivo area under the curve-fold increases of EP in humans. The Rb values for the drugs listed above were 2.17, 2.24, 4.90, and 1.04, respectively, and the in vivo area under the curve-fold increases of EP by these drugs were 2.87, 2.24, 5.39, and 1.98, respectively.

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: ophogen naar actie Ja, tevens fluconazol en verapamil koppelen.

PubMed feb 2024: geen nieuwe hits op 3A4-remmers, behalve Hirai 2023.
Stockley online feb 2024: severe, avoid; geen nieuwe info. As the increase in the AUC of eplerenone with ketoconazole is so great, the manufacturers contraindicate concurrent use.

Mechanisme: eplerenon is substraat van CYP3A4 (en niet van P-gp).

ATV: Stockley verwijst naar algemene monografie. PubMed niets. Liverpool: Do Not Coadminister (echter quality of evidence 'very low'; coadministration has not been studied and is contraindicated.)

Risicofactoren	
Mitigerende factoren	

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