Macitentan + CYP3A4-remmers M1283

M6 = ACT-132577 = actieve metaboliet macitentan

Onderbouwend	Stof	Effect	Code
Atsmon J. Clin Pharmacokinet 2013;52:685-92.	macitentan + ketoconazol	- macitentan: toename Cmax 1.3x (van 227 naar 290 ng/ml) en AUC 2.3x (van 5759 naar 13343 ng*h/ml) - M6: afname Cmax, ratio 0.49 (van 178 naar 87.6 ng/ml) en AUC, ratio 0.74 (van 19749 naar 14682 ng*h/ml) Regime: macitentan 10 mg 1x op dag 1; ketoconazol 400 mg/dag gedurende dag 1-24, macitentan 10 mg 1x op dag 5; 10 vrijwilligers; two-period, randomized, open-label, crossover study. Auteurs: Macitentan can be administered concomitantly with CYP3A4 inhibitors without need for dose adjustment. The changes are not considered to be clinically significant: "the increase in AUC∞ was well below (approximately 8-fold) the AUC∞ that was observed with the well-tolerated single dose of 300 mg macitentan and similar to subjects treated with 30 mg macitentan in an earlier multiple-dose study."	3A
SPC Opsumit EPAR Opsumit 07/02/2014	macitentan + ketoconazol	toename macitentan blootstelling met ong. factor 2 in aanwezigheid van ketoconazol 400 mg 1dd; afname blootstelling aan actieve metaboliet met 26%. Verwachte toename bij gebruik van op fysiologie gebaseerde farmacokinetische modellering was ongeveer een factor 3 in aanwezigheid van ketoconazol 200 mg 2dd. p.32: Drug-drug interaction study. Enrolled: 12 healthy subjects. Evaluable PK: 10 macitentan-treated subjects. Evaluable safety: 10 macitentan-treated subjects (A), 11 macitentan-treated subjects (B). Demographics: Male, Caucasian Treatment A: single macitentan 10 mg capsule dose. B: ketoconazole 400 mg 1 dd for 24 days. Conco-mitant single oral macitentan 10 mg dose (day 5). Design: Open-label, 2-way crossover.	2A

Overig	Stof	Effect
SPC Opsumit + EPAR Opsumit	macitentan + CYP3A4-remmers	voorzichtigheid is geboden bij combinatie met krachtige CYP3A4-remmers. EPAR: no clinically relevant interactions were observed for macitentan and its active metabolite M6 with drugs that are inhibitors of CYP3A4. → GIC: EPAR wijkt af van SPC. EPAR p.48 - PK/PD results Pharmacokinetic analysis showed that exposure in terms of Ctrough to both ACT-064992 and ACT-132557 was dose-proportional over the dose range tested. Pharmacodynamic results showed a pronounced effect on endothelin-1 levels in the 3- and 10-mg ACT-064992 dose groups. When pharmacokinetic (PK) and SiDBP at trough data are included in a mathematical model, the 10 mg dose seemed to be close to the plateau of the pharmacological effect. Safety: In study AC-055-201 in patients with essential hypertension, there were five cases of increases in liver transaminases >3×ULN, which led to the sponsor's decision to end the study earlier than planned.
Weiss J. Eur J Pharmacol 2013;701:168-75.	macitentan	in vitro studies: - induceert mRNA expressie van CYP3A4, P-glycoprotein (P-gp, ABCB1), solute carrier of organic anions 1B1 (SLCO1B1), en uridinediphosphate-glucuronosyltransferase 1A3 (UGT1A9). - remt P-gp, BCRP, SLCO1B1, en SLCO1B3; matige remmer van CYP3A4 en CYP2C19. In conclusion our data provide a comprehensive analysis of the interaction profile of macitentan with drug metabolising and transporting enzymes in vitro. Although macitentan has a similar or higher potency for induction and inhibition of drug metabolising enzymes and transporters than bosentan, its low plasma concentrations and minimal accumulation in the liver suggest that it will be markedly less prone to drug-drug interactions than bosentan.

Opmerkingen
WFG: actie Nee, kennelijk middel met grote therapeutische breedte, zie Atsmon 2013. De vraag is ook wat/hoe je zou moeten monitoren. Je mag verwachten dat de voorschrijver van macitentan weet waar deze op moet letten. Het is geregistreerd bij pulmonale arteriële hypertensie, maar wordt ook wel toegepast bij sclerodermie. Conform afspraak standaardlijst CYP3A4-remmers koppelen. Macitentan wordt door CYP3A4 (99%) omgezet.

Stockley, Hansten, PubMed: --

Risicogroep	

	Interactie	Actie	Datum
Beslissing WFG	Ja	Nee	12 mei 2015