Bedaquiline + CYP3A4-remmers M1222

M2: actieve N-monodesmethyl metaboliet

Onderbouwend	Stof	Effect	Code
SPC + EPAR Sirturo	bedaquiline + ketoconazol	toename AUC bedaquiline met 22%; geen effect op Cmax en AUC M2; kleine afname AUC ketoconazol (inductie?) Regime: bedaquiline 400 mg/dag dag 1-14, ketoconazol 400 mg/dag op dag 12-14. Een meer uitgesproken effect op bedaquiline kan worden waargenomen tijdens langdurige combinatie met ketoconazol of andere CYP3A-remmers. EPAR: design of the study was not optimal.	2A
	bedaquiline + lopinavir/ritonavir	toename AUC bedaquiline 22-40%, afname AUC M2 met 39-62% Regime: bedaquiline 400 mg alleen en op dag 11 na start lopinavir/ritonavir 400/100 mg 2dd gedurende 24 dagen. Komt waarschijnlijk door ritonavir.	2A
van Heeswijk RP ea. J Antimicrob Chemother 2014 May 23. [Epub ahead of print] doi:10.1093/jac/dku171	bedaquiline + ketoconazol	review van fabrikant Janssen Ref. 52 (van Heeswijk 2007, abstract): -toename bedaquiline: AUC_{24} 22%, geen wijziging Cmax; M2: geen wijziging AUC_{24} en Cmax -afname ketoconazol Cmin 45%; geen wijziging AUC/Cmax Regime: bedaquiline 400 mg 1dd gedurende 14 dagen, ketoconazol 400 mg 1dd op dag 12-14; 16 gezonde vrijwilligers. Auteurs: the modest effect of ketoconazole on bedaquiline exposure could be misleading. It has been reported that shortterm DDI studies with compounds possessing long half-lives may result in underestimation of the potential effects of chronic coadministration of a metabolic inhibitor. Ref.19 (Sirturo FDA 2013): toename QTc-interval (5h postdose, herhaalde toed.) bij combinatie 28.3 ms alleen bedaquiline 16.4 ms; ketoconazol 7.6 ms	1A
	bedaquiline + lopinavir/ritonavir	Ref 45 (van Heeswijk 2010, abstract): bedaquiline: toename AUC_{336} 22%, geen wijziging Cmax; M2: afname AUC_{24} 41% en Cmax 51% Regime: bedaquiline 400 mg 1-malig, lopinavir/ritonavir 400/100 mg 2dd gedurende 10 dagen: 16 gezonde vrijwilligers.	1A

Overig	Stof	Effect
SPC + EPAR Sirturo	bedaquiline + CYP3A4-remmers	Vermijd combinatie met matige of krachtige CYP3A4-remmers (bv. ciprofloxacine, erytromycine, fluconazol, clarithromycine, ketoconazol, ritonavir) gedurende meer dan 14 opeenvolgende dagen vanwege het mogelijke risico op bijwerkingen. Igv combinatie wordt meer frequente controle met een ECG en bepaling van transaminasen aanbevolen.
	bedaquiline + QT	In een onderzoek werd een groter effect op QTc waargenomen na herhaalde dosering met de combinatie van bedaquiline en ketoconazol dan na herhaalde dosering met de geneesmiddelen afzonderlijk; frequente controle is aanbevolen. p.92 <u>QT-findings during therapy with bedaquiline:</u> In study C208 ECGs were followed at pre-specified time points. It was obvious that QTc-intervals increased significantly in the bedaquiline-group (vs placebo). In line with changes in liver enzymes there was a slow and gradual onset, maximum at around week 18, and stable until week 24 (here bedaquiline was stopped). The largest mean increase in QTcF was 15.7 ms in the bedaquiline group (at Week 18), versus 6.2 ms in the placebo group (at Week 18). 1 patient in the bedaquiline group showed a QTc > 500 ms (none in the placebo group). Similar increases in QTc were seen in study C209 (around + 15 ms). Here a significant finding was seen with regards to background regimen; increases were substantially larger in patients with concomitant clofazimine (n=13) (Week 24, 31.94 ms versus 12.28 ms in patients without that drug). Although bedaquiline does have an impact on QTc, changes as compared to placebo (background regimens very similar) are still moderate (mean difference around 10 ms at week 18, when maximum increase was achieved). Total increase, around 15 ms, is also moderate, although above the common threshold of 10 ms referred to in drug development. <u>Safety related to drug-drug interactions and other interactions</u> In all DDI studies, safety observations in the treatment phase in which the respective concomitant medication was co-administered with bedaquiline was comparable with those in the treatment phase where bedaquiline was administered alone. EPAR Table 36. Summary of the Safety Concerns, categorie ‘Missing information’: Drug-drug interactions with potent inhibitors of drug metabolising enzymes and transporters.
Arizona CERT. www.crediblemeds.org. Geraadpleegd 5 juni 2014.	bedaquiline + QT	bedaquiline staat op lijst Drugs with possible TdP risk.

Opmerkingen
Niet in Hansten, Stockley.

Risicogroep	

	Interactie	Actie	Datum
Beslissing WFG	Ja	Nee	1 juli 2014