Tofacitinib + CYP3A4-remmers/Fluconazol MFB 6054

Onderbouwend	Stof	Effect	Code
Gupta P. Clin Pharmacol Drug Dev 2014;3:72-7.	tofacitinib + ketoconazol tofacitinib + fluconazol	↑ AUC tofacitinib 2x, Cmax 1.2x, t½ 3 → 4 uur Regime: ketoconazol 400 mg op dag 1-3, tofacitinib 10 mg alleen en op dag 3 met ketoconazol, 12 vrijwilligers ↑ AUC tofacitinib 1.8x, Cmax 1.3x, t½ 3 → 4 uur Regime: fluconazol 400 mg op dag 1 en 200 mg/dag op dag 2-7, tofacitinib 30 mg alleen en op dag 5 met fluconazol; 12 vrijwilligers	3A
SPC + EPAR Xeljanz	tofacitinib + ketoconazol, fluconazol	↑ AUC tofacitinib 2x, Cmax 1.2x door ketoconazol ↑ AUC tofacitinib 1.8x, Cmax 1.3x door fluconazol GIC: afgeleid uit fig. 1, zie onderaan risicoanalyse; zelfde getallen als Gupta 2014.	2A

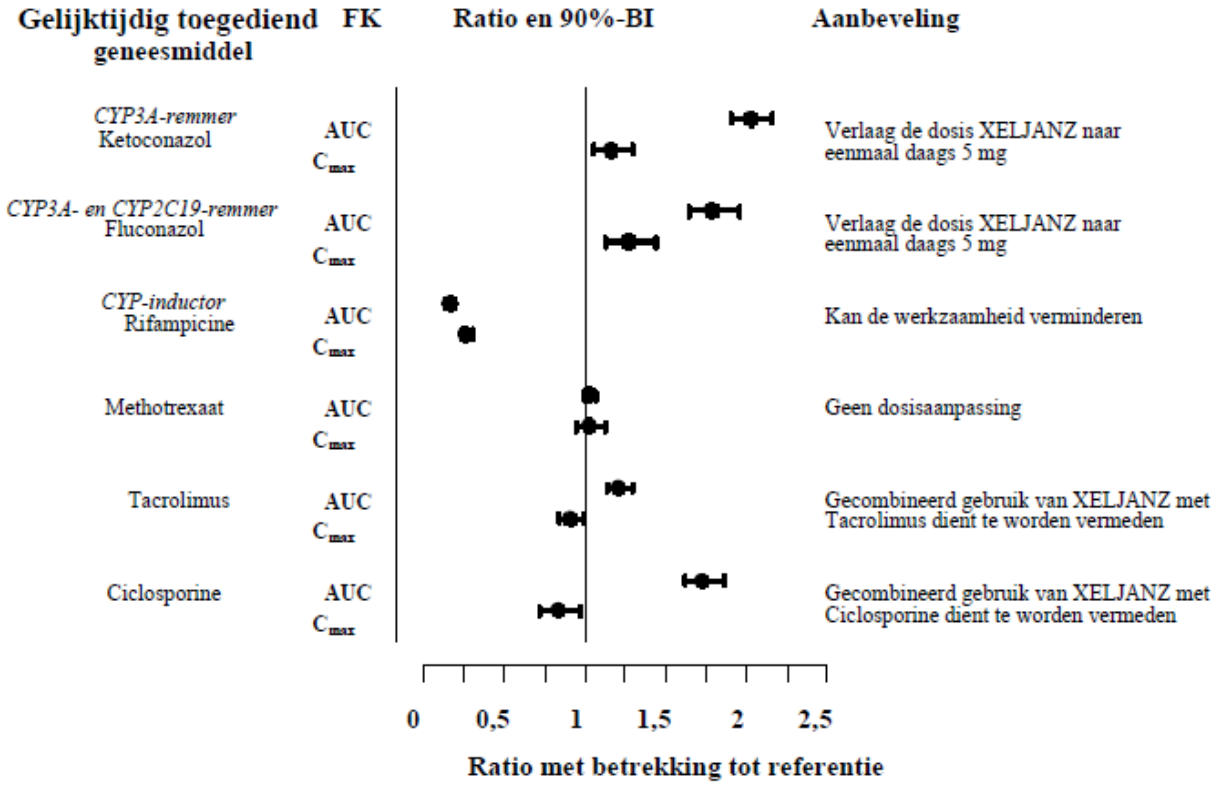
Overig	Stof	Effect
SPC + EPAR Xeljanz	tofacitinib + CYP3A4-remmers	gewoon preparaat: -verlaag tofacitinib naar 5 mg 1x per dag (bij gebruik van 5 mg 2x per dag) of naar 5 mg 2x per dag (bij gebruik van 10 mg 2x per dag) icm krachtige CYP3A4-remmers (bijv. ketoconazol). -verlaag naar 5 mg 1x per dag (bij gebruik van 5 mg 2x per dag) of naar 5 mg 2x per dag (bij gebruik van 10 mg 2x per dag) bij combinatie met matige CYP3A4-remmers die ook krachtig CYP2C19-remmen (bijv. fluconazol) preparaat met gereguleerde afgifte (mga) -verlaag tofacitinib naar 5 mg 1x per dag (gewoon preparaat) bij gebruik van 11 mg 1x per dag (preparaat mga).
Gupta P. Clin Pharmacol Drug Dev 2014;3:72-7.	tofacitinib + ketoconazol/ fluconazol	Different tofacitinib doses were employed (30 mg in fluconazole study vs. 10 mg in ketoconazole study). This was primarily due to timing of the studies relative to the clinical development of tofacitinib. The fluconazole study was performed prior to proof of concept (efficacy) data in the patient population when the therapeutic dose range was not established, while the ketoconazole study was performed after doses for Phase 3 studies in RA patients (5 and 10 mg BID) were selected. A single dose of 10 mg was chosen for the ketoconazole study as it was the lowest dose for which concentrations were measurable for 24 hours post-dose.
Krishnaswami S. Clin Pharmacol Drug Dev 2015;4:83-8.	tofacitinib	Single dose escalating study: no appreciable correlation was observed between tofacitinib dose and lymphocyte subset counts. Single-dose tofacitinib up to 100 mg in healthy subjects had a safety profile of mostly mild AEs, and no deaths, serious AEs, severe AEs/discontinuations due to AEs.
Song GG. J Intern Med 2014; 29:656–63.	tofacitinib	A systematic review of randomized controlled trials (RCTs) that examined the efficacy and safety of tofacitinib in patients with active RA was performed. The safety outcomes did not differ between the 5- and 10-mg and placebo groups with the exception of infection in the tofacitinib 10-mg group RR, 2.133; 95% CI, 1.268 to 3.590; p = 0.004). We did not directly compare the effects of tofacitinib at 5 and 10 mg twice per day. A dose-response relationship was not observed, and whether a dose of 10 mg twice daily is more effective than 5 mg is unclear.

Opmerkingen
Werkgroep Interacties 2-12-2019: bij fluconazol 150 mg 1-malig of 150 mg 1x per week is geen actie nodig.
Hansten top 100: fluconazol 100 mg/dag geeft weinig CYP3A4-remming; bij 200-400 mg/dag is dit meer.

Risicofactoren	
Mitigerende factoren	

	Interactie	**Actie**	**Datum**
Beslissing WG IA	Ja	Ja	2 december 2019

Figuur 1. Invloed van andere geneesmiddelen op de farmacokinetiek van XELJANZ



Opmerking: De referentiegroep kreeg alleen XELJANZ toegediend
FK = farmacokinetiek, BI = betrouwbaarheidsinterval

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