Acalabrutinib + Fluconazol/Isavuconazol | M 8569

ACP-5862 = actieve metaboliet van acalabrutinib

Onderbouwend	Stof	Effect	Code
Chen B. Br J Clin Pharmacol 2022;88:3716-29.	acalabrutinib + fluconazol, isavuconazol	-isavuconazol: acalabrutinib ↑least square means Cmax 1.37x and AUC 1.60x; ACP-5862 ↑0.72x resp. 0.91x; -fluconazol: ↑Cmax 1.48x and AUC 2.16x; ACP-5862 ↑0.65x resp. 0.95x. Methods: acalabrutinib 100 mg 1x with or without fluconazole 400 mg 1x; or isavuconazole 200 mg 3dd on day 1 and 200 mg 1dd day 2-5 and acalabrutinib 100 mg 1x on day 5; open label, randomized, 2-period study with 2x14 healthy volunteers. Experimental data were compared to PBPK simulation results. The PBPK model was able to recover acalabrutinib and ACP-5862 PK profiles in the study. Bruton tyrosine kinase receptor occupancy change was minimal in the presence of isavuco-nazole. There were no serious adverse events (AEs), or subject discontinuation due to AEs in this study. Only mild (Grade 1) AEs were reported during the study, by 17% of the study population. Conclusion: the results suggest that no dose adjustment is needed for concomitant administration with moderate CYP3A inhibitors.	3A
SPC Calquence	acalabrutinib + fluconazol, isavuconazol	↑Cmax en AUC acalabrutinib 1.4-2x maal; ↓Cmax en AUC van de actieve metaboliet ACP-5862 0.65-0.88x tov toediening van acalabrutinib alleen. Regime: gelijktijdige toediening met fluconazol 400 mg als enkele dosis of isavuconazol 200 mg als herhaalde dosis gedurende 5 dagen, bij gezonde proefpersonen. → GIC: lijkt op Chen 2022.	2A
Zhou D. CPT Pharmacometrics Syst Pharmacol 2019;8:489-99. PBPK =physiologically-based pharmacokinetic model	acalabrutinib + CYP3A4-remmers	acalabrutinib is a CYP3A substrate; the PBPK model predicted clinically observed acalabrutinib DDI with itraconazole (4.8-fold vs 5.2-fold observed). An increase of 2- to 3-fold acalabrutinib AUC was predicted for coadministration with moderate CYP3A inhibitors. When both the parent drug and active metabolite (total active components) were considered, the magnitude of the CYP3A DDI was much less significant.	1A

Overig	Stof	Effect
SPC Calquence	acalabrutinib + CYP3A-remmers	geen dosisaanpassing nodig bij combi met matige CYP3A-remmers. Monitor op bijwerkingen.
Calquence FDA label	acalabrutinib + matige CYP3A-remmers	co-administration with moderate CYP3A inhibitors (eg. Fluconazole) is predicted to increase acalabrutinib Cmax and AUC by approximately 2- to 3-fold. Reduce the dosage from 100 mg every 12 hours to 100 mg once daily.

Opmerkingen

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncolA	Ja	Nee	25-6-25