Zanubrutinib + Ciclosporine/Cimetidine/Fluvoxamine	M 8187

Onderbouwend	Stof	Effect	Code
SPC + EPAR Brukinsa PBPK: physiologically-based pharmacokinetic model	zanubrutinib + fluvoxamine, ciclosporine, cimetidine	↑AUC en Cmax zanubrutinib 1.5x door 'zwakke remmers' obv PBPK-model (fluvoxamine 50 mg QD, cyclosporine 200 mg QD) and cimetidine (400 mg BID)	1A
Wang K. CPT Pharmacometrics Syst Pharmacol 2021;10:441-54. PBPK: physiologically-based pharmacokinetic model	zabrutinib + remmers	PBPK model: model predictions were generally within 1.5-fold of the observed clinical data. The simulations indicated that strong, moderate, and mild CYP3A inhibitors may increase zanubrutinib exposures by approximately four-fold, two- to three-fold, and <1.5-fold, respectively.	0A

Overig	Stof	Effect
SPC + EPAR Brukinsa	zanubrutinib + zwakke CYP3A4-remmers	- zwakke CYP3A-remmers: geen dosisaanpassing vereist. Controleer op toxiciteit. p.36 BGB-3111 is a substrate of CYP3A4. p.62 Zanubrutinib as a victim of DDI of strong CYP3A4 inhibitor (itraconazole) was investigated in clinical Study BGB-3111-104. The model was used to predict DDI potential with strong, moderate and mild CYP3A4 inhibitors. Ongoing Study BGB-3111-113 will confirm the proposed dose recommendations for Z in the presence of strong (clarithromycin and voriconazole) and moderate (fluconazole and diltiazem) CYP3A inhibitors.
Brukinsa FDA prod.label	zabrutinib + remmers	hetzelfde advies als SPC
Zhang H. Pharmacol Res Perspect 2021;9:e00870.	zabrutinib	In vitro study. Phenotyping studies indicate CYP3A is the major CYP isoform responsible for zanubrutinib (Z) metabolism. Z showed mild reversible inhibition with half maximal inhibitory concentration (IC50) of 4.03, 5.69, and 7.80 μM for CYP2C8, CYP2C9, and CYP2C19, respectively. Data in human hepatocytes disclosed induction potential for CYP3A4, CYP2B6, and CYP2C enzymes. Transport assays demonstrated that Z is a potential substrate of P-gp. Additionally, Z is neither an inhibitor of P-gp at concentrations up to 10.0 μM nor an inhibitor of BCRP, OATP1B1, OATP1B3, OAT1, and OAT3 at concentrations up to 5.0 μM. The in vitro results were correlated with the available clinical DDIs using basic models and mechanistic static models. Z is not likely to be involved in transporter-mediated DDIs. CYP3A inhibitors and inducers may impact systemic exposure of Z.

Opmerkingen
Stockley: -

PubMed: verder niets.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncoIA	Ja	Nee	15 maart 2023