Fedratinib + Diltiazem/Fluconazol | MFB 7895

Onderbouwend	Stof	Effect	Code
SPC Inrebic PBPK: physiologically based pharmacokinetic model	fedratinib + diltiazem	↑AUC fedratinib 1.1x door diltiazem 120 mg 2dd Methode: PBPK-model met fedratinib 400 mg 1dd bij steady state.	1A
Wu F. Cancer Chemother Pharmacol 2020;86:461-73. doi: 10.1007/s00280-020-04131-y.	fedratinib + remmers	PBPK model simulations indicated that the fedratinib AUC at steady state is about 1.2-fold when moderate CYP3A4 inhibitors are co-administered with repeated doses of fedratinib. Methods: the PBPK model was constructed in Simcyp® by integrating in vitro and in vivo information and was further parameterized and validated by using clinical PK data.	0-1A

Overig	Stof	Effect
SPC Inrebic	fedratinib + CYP3A4-remmers	matige CYP3A4-remmer (erytromycine, diltiazem): monitor bij langdurig gebruik, pas zo nodig dosis aan op grond van bijwerkingen
SPC + EPAR Inrebic	fedratinib + gemengde remmer CYP3A4/ 2C19 fedratinib + fluconazol	niet onderzocht, maar obv PBPK-model ↑AUC fedratinib 4x door gemengde remmer CYP3A4/2C19 (zoals fluconazol). Vermijden. EPAR p.59: an in vivo DDI with the dual CYP2C19/3A4 inhibitor fluconazole or upon simultaneous inhibition of CYP3A4 and 2C19 by separate inhibitors cannot be excluded based on the in vitro data. Indeed, an interaction was predicted based on a PBPK Study, however, the PBPK model was not validated for CYP2C19. The applicant stated that these potential interactions will be further investigated in dedicated DDI studies. The submission of these studies is awaited. It is agreed that until data from this DDI study are received, dual CYP2C19 and CYP3A4 inhibitors like fluconazole should be avoided in patients receiving fedratinib.

Opmerkingen
Werkgroep Interacties oncologische middelen 17-11-21: actie Nee voor fluconazol ondanks mogelijke ↑AUC 4x, er zijn alleen PBPK data en het gebruikte model was niet gevalideerd voor CYP2C19.

PubMed: verder niets

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncoIA	Ja	Nee	17 november 2021