Ivosidenib + CYP3A4-inductoren | M 8489

Onderbouwend	Stof	Effect	Code
Prakash C. Cancer Chemother Pharmacol 2020;86:619-632. doi: 10.1007/s00280-020-04148-3. Epub 2020 Sep 25	ivosidenib + rifampicine, evavirenz	uitkomsten voorspeld op basis van PBPK-model; ↓ AUC en Cmax ivosidenib door: - rifampicine: ↓AUC met 65% en Cmax met 9% (ivosidenib eenmalig); ↓AUC met 33% en Cmax met 19% (ivosidenib 30 dagen) - evavirenz: ↓AUC met 50% en Cmax met 6% (ivosidenib eenmalig); ↓AUC met 11% en Cmax met 7% (ivosidenib 30 dagen) Auteurs: a greater DDI effect on the kinetics of a single dose than that of multiple-dose ivosidenib was predicted. This result is plausible as the CYP3A4 activity has been induced to a significant extent as a result of multiple-dose administration of ivosidenib (which also induces CYP3A4); thus, the inducible effect as a result of rifampin appears to be diminished as the magnitude of enzyme induction is inversely related to the baseline levels of enzyme.	1A

Overig	Stof	Effect
SPC + EPAR Tibsovo	ivosidenib + CYP3A4-inductoren	geen klinische onderzoeken uitgevoerd naar de farmaco-kinetiek van ivosidenib door een CYP3A4-inductor. Combinatie met sterke CYP3A4-inductoren zal naar verwachting de plasmaconcentraties van ivosidenib verlagen en is gecontra-indiceerd. Prediction accuracy of PBPK modelling with respect to the induction of CYP3A4-mediated DDIs was assessed considering twenty clinical studies. In these studies, the inducers of CYP3A4 were rifampicin, carbamazepine, phenobarbital, efavirenz and rifabutin. In 100% and 75% of the cases, the predicted mean AUC and Cmax ratios were within the criteria described. This result suggests that the PBPK platform is unable to accurately address Cmax ratios in 25% of the cases of the DDI mediated by CYP3A4 induction.
EPAR Tibsovo	ivosidenib	ivosidenib extensively becomes metabolised, mainly by oxidation by CYP3A4 (minor CYP2B6 and CYP2C8) and other CYP enzymes but also by N-dealkylation and conjugation with glutathione, cysteine or glucuronic acid. However, no circulation major metabolites were identified. In plasma the predominant compound is unchanged ivosidenib. Ivosidenib auto-induced its own metabolism at steady-state. For both indications no evidence of a clear relationship between a PK exposure parameter (presently AUC) and any of the investigated efficacy/safety endpoints was found.

Opmerkingen
Werkgroep Interacties Oncologische middelen: actie Ja, ook al zijn er uitsluitend PBPK data; bij intermitterend gebruik (bij AML) ivosidenib geen andere actie, is speculatie van de auteurs (Prakash 2020) en 'tegen intuïtief'. Standaardlijst CYP3A4-inductoren koppelen, ivosidenib wordt voornamelijk gemetaboliseerd via CYP3A4.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG Onco IA	Ja	Ja	2 oktober 2024