KNMP

Ivosidenib + CYP3A4-remmers/Fluconazol | M 8488

Onderbouwend	Stof	Effect	Code
Dai D. Eur J Clin Pharmacol 2019;75:1099-1108. doi: 10.1007/s00228-019-02673-6.	ivosidenib + itraconazol	↑AUC ivosidenib 2.7x en t1/2 van 60.7 naar 140.2 h door itraconazol; geen verandering Cmax. Regime: periode 1 ivosidenib 250 mg eenmalig, periode 2 itraconazol 200 mg 1 dd op dag 1-18, ivosidenib 250 mg eenmalig op dag 5. Studie onder 22 gezonde personen. Auteurs: When co-administration of ivosidenib with a strong CYP3A4 inhibitor is unavoidable, monitoring for QT interval prolongation is recommended and ivosidenib dose interruption or reduction may be considered.	3A
SPC + EPAR Tibsovo	ivosidenib + itraconazol ivosidenib + fluconazol	resultaten als Dai 2019. Combinatie met itraconazol verhoogde de ivosidenib (eenmalig) AUC 2.7x zonder verandering van de Cmax bij gezonde proefpersonen. EPAR p.57 The DDI study conducted with itraconazole following ivosidenib 250 mg administration which is half therapeutic dose, showed a 2.69 fold exposure (AUC) increase without affecting Cmax. These results could not be extrapolated to the therapeutic dose of 500 mg due to ivosidenib auto-induction. Collectively, the performed in vivo study and the PBPK model results provide some weight of evidence that interaction of ivosidenib at 500 mg with strong CYP3A4 inhibition is expected to increase ivosedenib exposure by two to three-fold. EPAR p.58 No formal interaction study of ivosidenib with moderate CYP3A4 inhibitor was conducted. However, the PBPK model predicted an AUC ratio of 1.90, and in addition PPK model showed fluconazole was a significant covariate associated with an AUC ratio of 1.69. In case of concomitant treatment with moderate CYP3A4 inhibitor, ivosidenib exposure increase is considered to be within two-fold.	2A
Prakash C. Cancer Chemother Pharmacol. 2020;86:619-632. doi: 10.1007/s00280-020-04148-3.	ivosidenib + itraconazol, ketoconazol, fluconazol	uitkomsten voorspeld op basis van PBPK-model; toename AUC en Cmax ivosidenib door: -itraconazol: AUC 2.14x, Cmax 1.04x (ivosidenib eenmalig); AUC 1.44x, Cmax 1.29x (ivosidenib 15 dagen) -ketoconazol: AUC 2.46x, Cmax 1.03x (ivosidenib eenmalig); AUC 3.23x, Cmax 2.26x (ivosidenib 15 dagen) -fluconazol: AUC 1.73x, Cmax 1.02x (ivosidenib eenmalig); AUC 1.90x, Cmax 1.52x (ivosidenib 15 dagen) Auteurs: these data suggest that the DDI effect of itraconazole on the kinetics of multiple-dose ivosidenib is smaller than that of single-dose ivosidenib. This result is plausible as the strong CYP3A4 induction effect as a result of multiple-dose administration of ivosidenib led to much lower itraconazole and its hydroxyl metabolite exposures, and lower inhibitory effects on	1A

		CYP3A4. Because itraconazole is a CYP3A4 substrate, the DDIs observed with itraconazole might not represent the magnitude of DDIs between ivosidenib and a strong CYP3A4 inhibitor that is not significantly metabolized by CYP3A4.	

Overig	**Stof**	**Effect**
SPC Tibsovo	ivosidenib + 3A4-remmers	vermijd combinatie met matige of sterke CYP3A4-remmers. Dit kan het risico van verlenging van het QTc-interval verhogen. Indien niet mogelijk: verlaag dosis ivosidenib naar 250 mg 1 dd, controleer op verlenging van het QTc-interval. Ivosidenib induceert CYP3A4, Itraconazol of ketoconazol dienen niet gelijktijdig met Tibsovo te worden gebruikt vanwege het verwachte verlies van werkzaamheid.
EPAR Tibsovo	ivosidenib	ivosidenib is extensively 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: standaardlijst CYP3A4-remmers koppelen, ivosidenib wordt voornamelijk gemetaboliseerd door CYP3A4. Fluconazol ook koppelen, de toename 1.9x is wel klinisch relevant.

Risicofactoren	
Mitigerende factoren	

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