Nierfunctie: fedratinib 7365

Clcr = creatinineklaring, AUC = Area Under the Curve

Onderbouwend	Bewijs	Effect	Opmerkingen
Ogasawara K ea. Pharmacokinetics and tolerability of fedratinib, an oral, selective Janus kinase 2 inhibitor, in subjects with renal or hepatic impairment. Cancer Chemother Pharmacol. 2020;85:1109-17.	3	Clcr 30-50 ml/min (n=8): AUC_{tot} 1,5x, AUC_{fu} 1,1x en Cmax 1,4 x verhoogd; Clcr 15-30 ml/min (n=7): AUC_{tot} 1,9x, AUC_{fu} 1,3x en Cmax 1,8 x verhoogd; tov personen met normale nierfunctie na 1-malig fedratinib 300 mg.	Auteurs: Clcr 15-30 ml/min: 200 mg per dag One possible explanation is that the reduced fu (as a result of increased protein binding in subjects with renal impairment) decreased fedratinib clearance and volume of distribution at steady state, which led to higher fedratinib exposure. Clcr geschat met Cockroft-Gault.
SPC Inrebic + EPAR Inrebic 03-03-2021. Zelfde getallen als Ogasawara 2020.	0	Clcr 30-59 ml/min (n=8): AUC 1,5x en Cmax 1,4x verhoogd; Clcr 15-29 ml/min (n=7): AUC 1,9x en Cmax 1,8 verhoogd tov personen met normale nierfunctie na 1-malig fedratinib 300 mg. In een populatie-PK-model was bij myelofibrosepatienten met Clcr 60-89 ml/min de AUC met 10% (klinisch niet relevant) en bij Clcr 30-59 ml/min met 37% verhoogd.	Clcr 15-29 ml/min: startdosis 200 mg per dag Clcr 30-89 ml/min: het kan nodig zijn om ten minste wekelijks te monitoren op veiligheid en, indien nodig, de dosis aan te passen op geleide van bijwerkingen Clcr geschat met Cockroft-Gault.

Overig	Opmerkingen
SPC Inrebic + EPAR Inrebic 03-03-2021	Discussion on clinical pharmacologyThe applicant argues that the 1.5-fold increased fedratinib exposure in patients with moderate renal impairment is not clinically relevant, based on comparable frequencies and distributions of treatment-emergent adverse events (TAEAs) in the pivotal Phase 3 trial EFC12153 (no of patients with normal renal function, n=57; mild/moderate impairment, n=128). This is agreed. However, in the absence of reassuring safety data for patients with severe renal impairment, a 2-fold dose-reduction is proposed for such patients which is acceptable. Safety in special populations In safety Pool #1, patients with mild/moderate baseline renal function were 135/203 in the 400 mg group and 218/321 (68%) overall. In general, the frequency and distribution of TEAEs was similar in subjects with normal or impaired renal function at baseline and similar relationships were observed when comparing the placebo and fedratinib treatment groups.

Risicogroep	

Opmerkingen:

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	Wijziging kinetiek	Actie	Clcr grens	Datum
Beslissing werkgroep	Ja	Ja	30 ml/min	27 september 2021