Nierfunctie: riociguat 5695

Clcr = creatinineklaring

Onderbouwend	Bewijs	Effect	Opmerkingen
SPC Adempas 7-11-2014.	0	AUC riociguat hoger bij patiënten met verminderde nierfunctie tov personen met normale nierfunctie: bij Clcr 50-80 ml/min 53% bij Clcr 30-50 ml/min 139% bij Clcr < 30 ml/min 54%	gegevens over patiënten met Clcr < 30 ml/min zijn beperkt; gebruik wordt niet aanbevolen. Risico op hypotensie is hoger bij patiënten met nierinsufficiëntie; daarom dosistitratie extra voorzichtig uitvoeren. Vanwege de hoge binding aan plasma-eiwitten is riociguat naar verwachting niet dialyseerbaar
FDA Draft briefing document for the cardiovascular and renal drugs advisory committee (CRDAC). 6-8-2013. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM363541.pdf geraadpleegd 12-8-2015	0	**CHEST-1**: Randomized, double-blind, placebo-controlled, multicentre, multi-national study to evaluate the efficacy and safety of oral riociguat (0.5 mg, 1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The mean half-life of riociguat was prolonged in all subjects with renal impairment (9.5 to 11.4 hours) compared to results in healthy subjects (6.2 hours). Likewise, the mean half-life of M1 (BAY 60-4552) was also longer in all subjects with renal impairment (22.6-31.0 hours) compared to results in healthy subjects (13.9 hours). The impact of renal insufficiency on riociguat exposure, by severity of renal impairment, is shown in the table below.	No dose adjustments are necessary in renal impairment The most prominent concern for overdose is drug-induced hypotension, which was seen in the overdose experience in trial12166 PH patients showed about 3 times higher AUC/D than healthy subjects after single dose administration of riociguat oral solution, most likely as a function of disease-inherent impaired elimination/excretion. The difference was statistically significant.
FDA Draft briefing document for the cardiovascular and renal drugs advisory committee (CRDAC). 6-8-2013. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM363541.pdf geraadpleegd 12-8-2015	0	**PATENT-1**: Randomized, double-blind, placebo-controlled, multi-centre, multi-national study to evaluate the efficacy and safety of oral riociguat (0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg tid) in patients with symptomatic pulmonary arterial hypertension (PAH). The effect of renal impairment was assessed following administration of a single dose of 1 mg of riociguat (15000) conducted in subjects with mild, moderate, and severe renal impairment. This study as conducted in non-smokers. A 200% increase in the total systemic exposure (AUC) to riociguat was observed in subjects with impaired renal function. A graded increase in AUC, reaching 200% in subjects with severe renal impairment was seen with M1. Peak plasma concentrations (Cmax) of riociguat or M1 were not significantly affected. Increased systemic exposure to riociguat and M1 may result in an increased drop in blood pressure eventually affecting tolerability and the ability to uptitrate dose. About 60% of the subjects in PATENT-1 had mild to moderate renal impairment at baseline. Of the subjects randomized to	These data suggest that there does not appear to be a lack of tolerability to dose uptitration in individuals with impaired renal function. Therefore, dose adjustments are not required in this population.

		the 1.0 to 2.5 mg individual titration arm, about 70-77% who had mild or moderate renal impairment at baseline had their dose uptitrated to 2.5 mg by end of study. In comparison about 80% of the subjects with normal renal function at baseline had their dose uptitrated to 2.5 mg by end of study.	

Table 5: Riociguat exposure in renal impairment (dose and weight normalized AUC [AUC_{norm}]; all subjects valid for PK, summary of clinical pharm studies table 1-3 pg 21)

Intrinsic factors	Ratio	Point estimate	90% confidence interval lower	upper
Renal Function	50 - 80 / >80 mL/min	1.4276	0.8714	2.3388
(groups acc. to	30 - <50 / >80 mL/min	2.0429	1.2570	3.3201
CL_{CR} at baseline)	<30 / >80 mL/min	1.4402	0.8862	2.3407

CL_{CR} = creatinine clearance

Source: Study 15678 [PH-36803 in Module 5.3.3.3; Table 14.4 / 4.2]

Risicogroep	

Opmerkingen:

- PubMed search 12-8-2015: geen gegevens.

<u>Clcr < 10 ml/min:</u>

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	Wijziging kinetiek	Actie	Clcr grens	Datum
Beslissing werkgroep	Ja	Nee	-	16 februari 2016

Raadpleegtekst	