PHARMACOKINETICS OF DARIFENACIN, AN M_3 SELECTIVE RECEPTOR ANTAGONIST: EFFECTS OF RENAL OR HEPATIC IMPAIRMENT

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Darifenacin is an M_3 selective receptor antagonist (M_3 SRA) for once daily treatment of overactive bladder. The effect of impaired renal or hepatic function on the steady-state pharmacokinetics of darifenacin 15 mg controlled release tablets, administered once daily for 6 days, was determined in 24 and 41 subjects, respectively.

Renal impairment had no clinically relevant effect on the pharmacokinetics of darifenacin (see Table 1 for mean values at day 6). Regression analysis showed that there was no relationship between darifenacin clearance and renal function. Plasma protein binding of darifenacin was not reduced in subjects with renal impairment.

Table 1

[a]**Parameter**	**Creatinine clearance (ml min^{-1})**			
	Normal (n = 6) (>80)	**Mild (n = 6) (51–80)**	**Moderate (n = 6) (30–50)**	**Severe (n = 6) (<30)**
AUC(0,24 h) (ng ml^{-1} h)	44.5	86.1	116	52.9
C_{max} (ng ml^{-1})	3.03	5.21	8.35	5.46
CL/F (l h^{-1})	337	174	129	284
CL_R (l h^{-1})	6.66	5.65	1.46	0.65
t_{max} (h)	6.3	6.7	5.2	5.4

[a]Data expressed as geometric means except for t_{max} which is the arithmetic mean.

There were no clinically important differences between subjects with mild hepatic impairment (Child Pugh A) and healthy controls. However, darifenacin exposure was increased in subjects with moderate hepatic impairment (Child Pugh B) (see Table 2). Following correction for protein binding, subjects with moderate hepatic impairment exhibited a mean 4.7-fold and 4.0-fold increase in unbound darifenacin AUC and C_{max}, respectively, compared with healthy controls.

Table 2

[a]**Parameter**	**Healthy (n = 12)**	**Child Pugh A (n = 13)**	**Child Pugh B (n = 11)**
AUC(0,24 h) (ng ml^{-1} h)	101	65	269
C_{max} (ng ml^{-1})	6.0	4.0	14.2
CL/F (l h^{-1})	149.1	229.4	55.7
t_{max} (h)	10.0	9.3	11.3

[a]Data expressed as geometric means except for t_{max} which is the arithmetic mean.

The safety profile was similar in healthy patients and patients with varying degrees of renal or hepatic impairment. In conclusion, these findings indicate no need for any specific changes to the proposed dosage regimen (7.5 mg or 15 mg once daily) for patients with renal impairment. While a dose of darifenacin CR 15 mg once daily can be used in mild hepatic impairment, the maximum recommended dose for use in subjects with moderate hepatic impairment is 7.5 mg once daily.