Table S1. UHPLC-ToF-MS Losartan and EXP3174 determination in acetonitrile HPLC grade (analytical method) and human plasma matrix (bioanalytical method) validation.

Losartan - Validation parameters ng/mL		Analytical validation		Bioanalytical validation	
Linearity (n = 3)		R^2: 1.00000		R^2: 0.99689	
		$y = 2*10^7x - 9021.5$		$y = 0.5862x + 2.641$	
Sensitivity		LoQ: 5		LoQ: 5	
		LoD: 2		LoD: 0.5	
		% ± SD		% ± SD	
Accuracy (n = 9)	[1,510]	92.8 ± 0.05	[750]	81.33 ± 0.20	
	[750]	102.69 ± 0.03	[150]	86.67 ± 0.05	
	[25]	99.4 ± 0.0007	[30]	133.3 ± 0.06	
		Mean ± %CV		Mean ± %CV	
Precision (n= 9)	[1,510]	1.39 ± 4.22	[750]	0.61 ± 0.20	
	[750]	0.770 ± 4.89	[150]	0.13 ± 0.05	
	[25]	0.025 ± 3.08	[30]	0.17 ± 1.33	
		%Change			
Robustness (n = 3)	[750][a]	-5.26			
	[750][b]	-14.57			
				% after 8h	% after 24h
Ice-thaw cicle			[750]	127.16	107.42
			[30]	127.90	114.32

EXP3174 - Validation parameters ng/mL		Analytical validation		Bioanalytical validation	
Linearity (n = 3)		R^2: 0.9966		R^2: 0.99843	
		$y = 1*10^7x - 257159$		$y = 0.1825x + 0.09865$	
Sensitivity		LoQ: 10		LoQ: 5	
		LoD: 4		LoD: 2	
		% ± SD		% ± SD	
Accuracy (n = 9)	[2,775]	91.58 ± 0.04	[925]	82.16 ± 0.23	
	[925]	89.42 ± 0.02	[185]	91.89± 0.08	
	[278]	88.85 ± 0.001	[37]	108.11 ± 0.10	
		Mean ± %CV		Mean ± %CV	
Precision (n= 9)	[2,775]	2.541 ± 1.59	[925]	0.76 ± 0.23	
	[925]	0.827 ± 3.29	[185]	0.17 ± 0.08	
	[278]	0.247 ± 0.50	[37]	0.04 ± 0.10	
Robustness (n = 3)	[925[a]]	%Change -6,80			
	[925[b]]	-10,8			
				% after 8h	% after 24h
Ice-thaw cicle			[925]	124.21	89.79
			[37]	111.41	104.25

[a]Acetronitrile HPLC supra gradient grade, [b]non-agitated.

Table S2. Plasmatic levels of Losartan and EXP3174 of hypertensive and CKD volunteers.

PATIENT SAMPLE	LOSARTAN (ng/mL)		EXP3174 (ng/mL)	
SAH	Before administration	After administration	Before administration	After administration
H1	-	56	8	72
H2	-	88	8	46
H3	-	12	30	22
H4	-	64	48	88
H5	-	76	14	24
H6	-	48	-	44
H7	-	72	-	22
H8	-	40	-	12
H9	-	54	8	40
H10	58	-	112	22
H11	-	80	-	14
H12	-	82	-	228[1]
H13	-	-	-	-
H14	-	100	26	118
H15	-	72	-	14
H16	-	152	14	48
H17	-	164	8	12
H18	-	62	2	10
H19	-	-	-	-
H20	10	178	210[1]	444[1]
H21	-	-	-	-
H22	74	70	156	336[1]
CKD	Before administration	After administration	Before administration	After administration
OUT (CKA)				
A1	290[1]	4	469.6[1]	18
A2	2	4	198	242[1]
A3	296[1]	6	182	26
A4	582[1]	26	18	14
A5	38	-	26	24
DIA[2] (CKN)				
N1	-		-	
N2	-		-	
N3	-		16	

N_4	-	26
N_5	252[1]	38
N_6	-	-
N_7	-	-
N_8	-	48
N_9	-	56
N_{10}	-	6
N_{11}	30	150
N_{12}	-	-
N_{13}	-	-
N_{14}	18	192

Results were calculated using the calibration curve and expressed as mean (in ng/mL). Therapeutic range of losartan: 200 – 650ng/mL and EXP3174: 200 – 1200ng/mL; OUT – outpatients; DIA – undergoing hemodyalisis; - Not detected; [1]reached the therapeutic range; [2]a single blood collection was performed 24h after drug administration in nephropathic patients undergoing hemodialysis. H_1-H_{22}: Hyperthensive patients, A_1-A_5: Nephropatic outpatients, N_1-N_{14}: Nephropatic patients undergoing dyalitic treatment.