

Supplementary Materials: Population Pharmacokinetic Analysis of Perampanel in Portuguese Patients Diagnosed with Refractory Epilepsy

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Table S1 – Demographic and pharmacotherapeutic characteristics of the patients included in the study.

Patient	Sex	Age (years)	BW (kg)	HT (cm)	BSA (m ²)	BMI (kg/m ²)	Daily dose of perampanel (mg)	Co-prescribed ASD
1	Male	26	76	182	1.97	22.94	4	CLB, LEV, ZNS
2	Male	54	70	167	1.79	25.10	4	CBZ
3	Male	49	87	171	1.99	29.75	4	LEV
4	Male	26	45	168	1.49	15.94	4	LEV
5	Male	21	48	160	1.48	18.75	4	VA, CBZ, CLB, ZNS
6	Male	20	78	176	1.94	25.18	6	ESL, LEV
7	Female	57	55	167	1.61	19.72	6	CBZ, LEV
8	Male	20	72	180	1.91	22.22	4	VA, LEV
9	Female	23	83	166	1.91	30.12	6	CLB, LEV
10	Male	39	98	175	2.13	32.00	4	VA, LEV
11	Male	26	79	178	1.97	24.93	10	CLB, LAC, LEV
12	Female	21	57.5	160	1.59	22.46	8	CLB, LEV, OXC
13	Male	47	79	179	1.98	24.66	2	VA, ESL, LAC, LEV
14	Male	38	90	178	2.08	28.41	6	ESL, LEV
15	Male	76	80	175	1.96	26.12	4	LEV
16	Male	46	84	183	2.06	25.08	10	CBZ, LAC
17	Male	53	99	185	2.23	28.93	10	CBZ, CLB, LEV
18	Female	21	65	168	1.74	23.03	8	VA
19	Male	52	59	169	1.68	20.66	8	ESL, LTG
20	Female	26	95	162	1.99	36.20	10	CBZ, CLB, LAC, LEV
21	Male	25	85	188	2.11	24.05	8	CBZ, LTG
22	Male	27	84	181	2.05	25.64	8	ESL, PB, PHT, LEV
23	Male	30	59	163	1.63	22.21	8	LEV
24	Female	41	77	162	1.82	29.34	6	VA, LEV, TPM

25	Female	32	75	167	1.84	26.89	4	TPM
26	Male	55	97	169	2.07	33.96	8	CBZ
27	Female	54	62	158	1.63	24.84	8	CBZ, LAC, LEV
28	Female	43	69	158	1.71	27.64	6	OXC, TPM
29	Male	28	45	169	1.49	15.76	6	LEV
30	Female	44	80	155	1.79	33.30	6	CBZ, LEV, TPM
31	Female	23	55	176	1.68	17.76	6	LEV, ZNS
32	Female	23	53	158	1.52	21.23	10	CLB, LTG
33	Male	44	90	170	2.01	31.14	4	CBZ, ESL, LEV
34	Male	31	60	160	1.62	23.44	6	VA, LEV
35	Female	42	58	163	1.62	21.83	4	CBZ, CLB, ZNS
36	Male	56	94	169	2.04	32.91	8	CBZ, ZNS
37	Female	25	93.5	164	1.99	34.76	6	ESL, LEV
38	Female	34	65	164	1.71	24.17	4	-
39	Male	53	61	163	1.66	22.96	8	ESL, LTG
40	Male	64	85	175	2.01	27.76	4	CBZ, PB, LEV
41	Male	19	95	194	2.27	25.24	10	CLB, ESL, ZNS
42	Female	67	82	157	1.83	33.27	6	VA, LEV, TPM
43	Female	23	63	155	1.62	26.22	4	CBZ, CLB, PHT, LTG
44	Male	27	90	180	2.10	27.78	8	ESL, PB, LEV

BW, Body weight; BMI, body mass index; BSA, body surface area; CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; HT, height; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; VA, valproic acid, ZNS, zonisamide.

Table S2 – Covariates tested for volume of distribution.

Model	Covariates	Parameters	OBJ	ΔOBJ
Base	TVCL=THETA(1) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10	765.384	-
1	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)*BW)	THETA(1)=0.666 THETA(2)=3.84 THETA(3)=0.107	753.456	ΔOBJ ₁₋₀ = -11.928
2	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)*BSA)	THETA(1)=0.669 THETA(2)=24.60 THETA(3)=0.687	760.205	ΔOBJ ₂₋₀ = -5.179
3	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)*BMI)	THETA(1)=.668 THETA(2)=6.61 THETA(3)=0.184	754.178	ΔOBJ ₃₋₀ = -11.206
4	TVCL=THETA(1) TVV=THETA(2)*((BW/77.5)**THETA(3))	THETA(1)=0.663 THETA(2)=32.00 THETA(3)=1.55	750.765	ΔOBJ ₄₋₀ = -14.619
5	TVCL=THETA(1) TVV=THETA(2)*((BSA/1.9)**THETA(3))	THETA(1)=0.666 THETA(2)=32.00 THETA(3)=1.99	758.045	ΔOBJ ₅₋₀ = -7.339
6	TVCL=THETA(1) TVV=THETA(2)*((BMI/25.1)**THETA(3))	THETA(1)=0.665 THETA(2)=29.60 THETA(3)=2.07	747.792	ΔOBJ ₆₋₀ = -17.592
7	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)**SEX)	THETA(1)=0.672 THETA(2)=33.40 THETA(3)=0.971	765.363	ΔOBJ ₇₋₀ = -0.021
8	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)*TP)	THETA(1)=0.671 THETA(2)=12.80 THETA(3)=0.357	764.979	ΔOBJ ₈₋₀ = -0.405
9	TVCL=THETA(1) TVV=THETA(2)*((TP/7.0)**THETA(3))	THETA(1)=0.671 THETA(2)=32.00 THETA(3)=0.942	764.977	ΔOBJ ₉₋₀ = -0.407
10	TVCL=THETA(1) TVV=THETA(2)*(THETA(3)*ALB)	THETA(1)=0.671 THETA(2)=16.20	766.254	ΔOBJ ₁₀₋₀ = +0.87

		THETA(3)=0.451		
11	TVCL=THETA(1) TVV=THETA(2)*((ALB/4.4)**THETA(3))	THETA(1)=0.672 THETA(2)=33.10 THETA(3)=0.008	765.386	$\Delta\text{OBJ}_{11-0} = +0.002$
12	TVCL=THETA(1) TVV=THETA(2)*((AGE/33)**THETA(3))	THETA(1)=0.672 THETA(2)=33.10 THETA(3)=0.038	765.364	$\Delta\text{OBJ}_{12-0} = -0.02$

ALB, serum albumin; BW, Body weight; BMI, body mass index; BSA, body surface area; OBJ, objective function value; TP, total proteins; TVCL, typical value of clearance; TVV, typical value of volume of distribution.

Table S3 – Covariates tested for clearance.

Model	Covariates	Parameters	OBJ	ΔOBJ	IPV
Base (0)	TVCL=THETA(1) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10	765.384	-	58.57%
1	TVCL=THETA(1)*(THETA(3)*BW) TVV=THETA(2)	THETA(1)=0.032 THETA(2)=33.30 THETA(2)=0.291	764.030	ΔOBJ ₁₋₀ = -1.354	57.71% (-0.86%)
2	TVCL=THETA(1)*(THETA(3)*BSA) TVV=THETA(2)	THETA(1)=0.502 THETA(2)=33.20 THETA(2)=0.730	763.392	ΔOBJ ₂₋₀ = -1.992	57.27% (-1.30%)
3	TVCL=THETA(1)*(THETA(3)*BMI) TVV=THETA(2)	THETA(1)=0.136 THETA(2)=33.30 THETA(2)=0.195	764.193	ΔOBJ ₃₋₀ = -1.191	57.79% (-0.78%)
4	TVCL=THETA(1)*((BW/77.5)**THETA(3)) TVV=THETA(2)	THETA(1)=0.699 THETA(2)=33.20 THETA(2)=0.611	763.079	ΔOBJ ₄₋₀ = -2.305	57.01% (-1.56%)
5	TVCL=THETA(1)*((BSA/1.9)**THETA(3)) TVV=THETA(2)	THETA(1)=0.698 THETA(2)=33.20 THETA(2)=1.070	763.383	ΔOBJ ₅₋₀ = -2.001	57.27% (-1.30%)
6	TVCL=THETA(1)*((BMI/25.1)**THETA(3)) TVV=THETA(2)	THETA(1)=0.668 THETA(2)=33.10 THETA(2)=0.623	763.486	ΔOBJ ₆₋₀ = -1.898	57.27% (-1.30%)
7	TVCL=THETA(1)*(THETA(3)**SEX) TVV=THETA(2)	THETA(1)=0.684 THETA(2)=33.10 THETA(2)=0.954	765.318	ΔOBJ ₇₋₀ = -0.066	58.57% (-0%)
8	TVCL=THETA(1)*((LDH/197.5)**THETA(3)) TVV=THETA(2)	THETA(1)=0.673 THETA(2)=33.10 THETA(2)=0.183	765.278	ΔOBJ ₈₋₀ = -0.106	58.48% (-0.09%)
9	TVCL=THETA(1)*((AST/17)**THETA(3)) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10 THETA(2)=0.008	765.436	ΔOBJ ₉₋₀ = -0.052	58.65% (+0.08%)
10	TVCL=THETA(1)*((ALT/20)**THETA(3)) TVV=THETA(2)	THETA(1)=0.675 THETA(2)=33.10	765.005	ΔOBJ ₁₀₋₀ = -0.379	51.31% (-7.26%)

		THETA(2)=0.103			
11	TVCL=THETA(1)*((AP/71)**THETA(3)) TVV=THETA(2)	THETA(1)=0.665 THETA(2)=33.00 THETA(2)=0.251	764.098	$\Delta\text{OBJ}_{11-0} = -1.286$	57.71% (-0.86%)
12	TVCL=THETA(1)*((GGT/36.5)**THETA(3)) TVV=THETA(2)	THETA(1)=0.689 THETA(2)=33.10 THETA(2)=0.297	758.381	$\Delta\text{OBJ}_{12-0} = -7.003$	54.04% (-4.53%)
13	TVCL=THETA(1)*((TB/0.45)**THETA(3)) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10 THETA(2)=0.008	765.565	$\Delta\text{OBJ}_{13-0} = +0.181$	58.74% (+0.17%)
14	TVCL=THETA(1)*((TP/7.0)**THETA(3)) TVV=THETA(2)	THETA(1)=0.664 THETA(2)=33.10 THETA(2)=1.24	764.793	$\Delta\text{OBJ}_{14-0} = -0.591$	52.22% (-6.35%)
15	TVCL=THETA(1)*((ALB/4.4)**THETA(3)) TVV=THETA(2)	THETA(1)=0.671 THETA(2)=33.10 THETA(2)=0.344	765.295	$\Delta\text{OBJ}_{15-0} = -0.089$	58.48% (-0.09%)
16	TVCL=THETA(1) TVV=THETA(2)*((AGE/33)**THETA(3))	THETA(1)=0.665 THETA(2)=33.10 THETA(3)=0.194	764.647	$\Delta\text{OBJ}_{11-0} = -0.737$	58.05% (-0.52%)
17	TVCL=THETA(1) TVV=THETA(2)* (THETA(3)*GFR)	THETA(1)=0.066 THETA(2)=33.10 THETA(3)=0.095	765.843	$\Delta\text{OBJ}_{17-0} = +0.459$	58.91% (+0.34%)
18	TVCL=THETA(1) TVV=THETA(2)* (THETA(3)*(GFR/110.6))	THETA(1)=0.690 THETA(2)=33.10 THETA(3)=1.000	765.843	$\Delta\text{OBJ}_{18-0} = +0.459$	58.91% (+0.34%)
19	TVCL=THETA(1) TVV=THETA(2)*((GFR/110.6)**THETA(3))	THETA(1)=0.681 THETA(2)=33.10 THETA(3)=0.437	764.675	$\Delta\text{OBJ}_{19-0} = -0.709$	58.14% (-0.43%)
20	TVCL=THETA(1) TVV=THETA(2)* (THETA(3)**(GFR/110.6))	THETA(1)=0.408 THETA(2)=33.10 THETA(3)=1.66	764.730	$\Delta\text{OBJ}_{20-0} = -0.654$	58.14% (-0.43%)

ALB, serum albumin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BW, Body weight; BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; IPV, interpatient variability; LDH, lactate dehydrogenase; OBJ, objective function value; TB, total bilirubin; TP, total proteins; TVCL, typical value of clearance; TVV, typical value of volume of distribution.

Table S4 – Antiseizure drugs tested for clearance.

Model	Covariates	Parameters	OBJ	ΔOBJ	IPV
Base (0)	TVCL=THETA(1) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10	765.384	-	58.57%
1	TVCL=THETA(1)*(THETA(3)**CBZ) TVV=THETA(2)	THETA(1)=0.961 THETA(2)=33.00 THETA(2)=0.498	758.814	ΔOBJ ₁₋₀ = -6.57	54.31% (-4.26%)
2	TVCL=THETA(1)*(THETA(3)**OXC) TVV=THETA(2)	THETA(1)=0.656 THETA(2)=33.10 THETA(2)=1.24	764.790	ΔOBJ ₂₋₀ = -0.594	58.22% (-0.35%)
3	TVCL=THETA(1)*(THETA(3)**PB) TVV=THETA(2)	THETA(1)=0.666 THETA(2)=33.10 THETA(2)=1.04	765.351	ΔOBJ ₃₋₀ = -0.033	58.57% (-0%)
4	TVCL=THETA(1)*(THETA(3)**PHT) TVV=THETA(2)	THETA(1)=0.641 THETA(2)=33.10 THETA(2)=1.99	761.397	ΔOBJ ₄₋₀ = -3.987	55.95% (-2.62%)
5	TVCL=THETA(1)*(THETA(3)**CLB) TVV=THETA(2)	THETA(1)=0.494 THETA(2)=32.80 THETA(2)=2.47	732.405	ΔOBJ ₅₋₀ = -32.979	40.00% (-18.57%)
6	TVCL=THETA(1)*(THETA(3)**ESL) TVV=THETA(2)	THETA(1)=0.611 THETA(2)=33.00 THETA(2)=1.46	761.848	ΔOBJ ₆₋₀ = -3.536	56.30% (-2.27%)
7	TVCL=THETA(1)*(THETA(3)**LAC) TVV=THETA(2)	THETA(1)=0.642 THETA(2)=33.30 THETA(2)=2.76	759.278	ΔOBJ ₇₋₀ = -6.106	54.59% (-3.98%)
8	TVCL=THETA(1)*(THETA(3)**LEV) TVV=THETA(2)	THETA(1)=0.663 THETA(2)=33.10 THETA(2)=1.13	765.180	ΔOBJ ₈₋₀ = -0.204	58.48% (-0.09%)
9	TVCL=THETA(1)*(THETA(3)**LTG) TVV=THETA(2)	THETA(1)=0.813 THETA(2)=33.10 THETA(2)=0.742	762.686	ΔOBJ ₉₋₀ = -2.698	56.83% (-1.74%)
10	TVCL=THETA(1)*(THETA(3)**TPM) TVV=THETA(2)	THETA(1)=0.670 THETA(2)=33.10	765.359	ΔOBJ ₁₀₋₀ = -0.025	58.57% (-0%)

		THETA(2)=1.07			
11	TVCL=THETA(1)*(THETA(3)**ZNS) TVV=THETA(2)	THETA(1)=0.685 THETA(2)=33.10 THETA(2)=0.852	765.056	$\Delta\text{OBJ}_{11-0} = -0.328$	58.31% (-0.26%)
12	TVCL=THETA(1)*(THETA(3)**VA) TVV=THETA(2)	THETA(1)=0.715 THETA(2)=33.10 THETA(2)=0.710	763.133	$\Delta\text{OBJ}_{12-0} = -2.251$	57.09% (-1.48%)
13	TVCL=THETA(1)*(THETA(3)**IND) TVV=THETA(2)	THETA(1)=0.427 THETA(2)=33.30 THETA(2)=2.71	711.125	$\Delta\text{OBJ}_{13-0} = -54.259$	31.09% (-27.48%)

CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; IND, enzyme-inducing antiseizure drugs; IPV, between-patient variability; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; OBJ, objective function value; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TVCL, typical value of clearance; TVV, typical value of volume of distribution; VA, valproic acid, ZNS, zonisamide.

Table S5 – Covariates tested for final model. At bold is the final model.

Model	Covariates	Parameters	OBJ	ΔOBJ	IPV
Base (0)	TVCL=THETA(1) TVV=THETA(2)	THETA(1)=0.672 THETA(2)=33.10	765.384	-	58.57%
1	TVCL=THETA(1)*(THETA(3)**IND) TVV=THETA(2)	THETA(1)=0.427 THETA(2)=33.30 THETA(3)=2.71	711.125	ΔOBJ ₁₋₀ = -54.259	31.09% (-27.48%)
2	TVCL=THETA(1)*(THETA(3)**IND)*(THETA(4)**CLB) TVV=THETA(2)	THETA(1)=0.417 THETA(2)=33.20 THETA(3)=2.64 THETA(4)=1.15	709.554	ΔOBJ ₂₋₁ = -1.571	30.56% (-28.01%)
3	TVCL=THETA(1)*(THETA(3)**IND) TVV=THETA(2)*((BMI/25.1)**THETA(4))	THETA(1)=0.419 THETA(2)=29.50 THETA(3)=2.76 THETA(4)=2.12	691.160	ΔOBJ₃₋₁= -19.965	30.82% (-27.75%)
4	TVCL=THETA(1)*(THETA(3)**IND)*((GGT/36.5)**THETA(5)) TVV=THETA(2)*((BMI/25.1)**THETA(4))	THETA(1)=0.427 THETA(2)=29.50 THETA(3)=2.67 THETA(4)=2.13 THETA(5)=0.057	690.454	ΔOBJ ₄₋₃ = -0.706	30.58% (-27.99%)
5	TVCL=THETA(1)*(THETA(3)**IND) *(THETA(5)**LAC) TVV=THETA(2)*((BMI/25.1)**THETA(4))	THETA(1)=0.420 THETA(2)=29.50 THETA(3)=2.77 THETA(4)=2.11 THETA(5)=0.978	691.137	ΔOBJ ₅₋₃ = -0.023	30.82% (-27.75%)

BMI, body mass index; CLB, clobazam; IND, enzyme-inducing antiseizure drugs; IPV, between-patient variability; GGT, gamma-glutamyl transferase; LAC, lacosamide; OBJ, objective function value; TVCL, typical value of clearance; TVV, typical value of volume of distribution.