

**Table 1.** Drug-dependent parameters values used for Levetiracetam on PBPK model

Parameter	Value	Reference
MW (g mol <sup>-1</sup> )	170.21	Drugbank*
logP	-0.67	<sup>25</sup>
pKa	15.74	<sup>25</sup>
Solubility (mg mL <sup>-1</sup> )	104.0	<sup>27</sup>
Specific intestinal permeability (x 10 <sup>-6</sup> cm s <sup>-1</sup> )	25.5	<sup>26,28</sup>
Fup (%)	90	<sup>23</sup> , Drugbank*
B:P	1.3	<sup>23</sup>
Adult		
$V_{ss}$ (L)	37.02	Calculated, <sup>29</sup>
Cl <sub>t</sub> (mL min <sup>-1</sup> kg <sup>-1</sup> )	0.92	<sup>27</sup>
Cl <sub>r</sub> (mL min <sup>-1</sup> kg <sup>-1</sup> )	0.63	<sup>13</sup>
GFR*fup (mL s <sup>-1</sup> )	0.8	Calculated
Pediatric 4-12		
$V_{ss}$ (L)	10.39	Calculated, <sup>29</sup>
Cl <sub>t</sub> ped (mL min <sup>-1</sup> kg <sup>-1</sup> )	1.43	<sup>14</sup>
Cl <sub>r</sub> ped (mL min <sup>-1</sup> kg <sup>-1</sup> )	0.95	Calculated
GFR*fup ped (mL s <sup>-1</sup> )	0.52	Calculated
Pediatric 0.5-3		
$V_{ss}$ (L)	6.04	Calculated, <sup>29</sup>
Cl <sub>t</sub> ped (mL min <sup>-1</sup> kg <sup>-1</sup> )	1.46	<sup>30</sup>
Cl <sub>r</sub> ped (mL min <sup>-1</sup> kg <sup>-1</sup> )	1.12	Calculated
GFR*fup ped (mL s <sup>-1</sup> )	0.30	Calculated

\*Drugbank accessed by <https://www.drugbank.ca/drugs/DB01202>: MW: molecular weight; logP: log of the octanol-water partition coefficient for the neutral compound; pka: acid dissociation constant; Fup: fraction unbound;  $V_{ss}$ : volume of distribution at steady state; B:P: plasma to blood ratio concentration, Cl<sub>t</sub>: total clearance from intravenous; Cl<sub>r</sub>: renal clearance ped: pediatrics.

**Table 2.** Observed data of plasma concentration of levetiracetam from scientific literature used in this work

<b>Dataset</b>	<b>Population</b>	<b>Age (years)</b>	<b>Dose (mg)</b>	<b>n</b>	<b>Route/ regimen</b>	<b>Reference</b>
Datasets for model building						
1	HV	30-40	1500	17	IV/S	<sup>27</sup>
2	HV	18-50	3500	8	Oral/S	<sup>13</sup>
Datasets for model validation						
3	HV	30-40	1500	17	Oral/S	<sup>27</sup>
4	HV	30-40	1500	12	IV/M	<sup>27</sup>
5	HV	40-54	500	12	IV/M	<sup>36</sup>
6	HV	18-50	500	8	Oral/S	<sup>13</sup>
7	HV	18-50	1000	8	Oral/S	<sup>13</sup>
8	HV	18-50	2000	8	Oral/S	<sup>13</sup>
9	HV	18-50	5000	8	Oral/S	<sup>13</sup>
10	HV	22-52	1500	16	Oral/S	<sup>37</sup>
11	Pediatric	06-12	20/kg	24	Oral/S	<sup>14</sup>
12	Pediatric	04-12	20/kg	21	Oral/S	<sup>38</sup>
13	Pediatric	04-12	40/kg	21	Oral/S	<sup>38</sup>
14	Pediatric	04-12	60/kg	21	Oral/S	<sup>38</sup>
15	Pediatric	0.5-02	20/kg	6	Oral/S	<sup>30</sup>
16	Pediatric	02-04	20/kg	3	Oral/S	<sup>30</sup>

**Table 3.** Pharmacokinetics parameters of Levetiracetam from predicted and observed data from different doses in adults (HV – health volunteers) and pediatric population.

Dat.	Age	Dose	Route/ regimen	OBS AUC	PRED AUC	MFE AUC	OBS C <sub>max</sub>	PRED C <sub>max</sub>	MFE C <sub>max</sub>	Ref
		mg		µg.h mL <sup>-1</sup>	µg.h mL <sup>-1</sup>		µg mL <sup>-1</sup>	µg mL <sup>-1</sup>		
1	30-40	1500	IV/S	392.4	378.0	0.96	50.50	55.12	1.09	27
2	18-50	3500	Oral/S	737.1	711.8	0.97	81.34	81.17	1.00	13
3	30-40	1500	Oral/S	427.9	307.0	0.71	47.70	32.51	0.68	27
4	30-40	1500	IV/M	371.9	390.0	1.04	71.00	67.30	0.94	27
5	40-54	500	IV/M	138.4	123.2	0.89	28.00	21.80	0.78	36
6	18-50	500	Oral/S	114.8	102.3	0.89	8.80	10.10	1.15	13
7	18-50	1000	Oral/S	199.3	216.5	1.09	23.23	22.70	0.98	13
8	18-50	2000	Oral/S	422.3	408.6	0.97	45.97	49.83	1.08	13
9	18-50	5000	Oral/S	1077.9	1020.7	0.95	115.70	115.40	1.00	13
10	22-52	1500	Oral/S	400.0	308.1	0.77	39.60	34.80	0.88	37
11	06-12	20/kg	Oral/S	248.2	214.9	0.87	22.7	28.5	1.26	14
12	04-12	20/kg	Oral/S	165.5	162.1	0.98	20.8	24.83	1.19	38
13	04-12	40/kg	Oral/S	384.3	486.2	1.27	49.6	60.15	1.21	38
14	04-12	60/kg	Oral/S	510	604.5	1.19	63.80	84.09	1.32	38
15	0.5-02	20/kg	Oral/S	239.0	137.76	0.57	27.32	27.46	0.99	30
16	02-04	20/kg	Oral/S	242.8	239.6	1.01	30.69	29.12	1.05	30

Dat: dataset; HV: Healthy adult volunteers; IV: intravenous bolus; S: single dose; M: multiple dose; Ped.: Pediatrics; OBS: Observed; PRED: Predicted

**Table 4.** Simulated mean maximum concentration (Cmax) and range from maximum concentration and minimum plasma concentration at Steady-state condition for pediatric population and their coefficient of variation (CV%).

Age (years) [weight] (kg)	Dose (mg kg <sup>-1</sup> day <sup>-1</sup> )	BID		TID	
		Cmax (µg mL <sup>-1</sup> )	Range [min and max] (µg mL <sup>-1</sup> )	Cmax (µg mL <sup>-1</sup> )	Range [min and max] (µg mL <sup>-1</sup> )
0.5 to 3 [8.29- 14.95]	10	6.78 [13.24 %]	4.68-7.58	4.59 [11.62%]	3.72-5.57
	20	13.71 [9.67%]	10.75-15.02	8.32 [14.38%]	7.04-11.88
	40	26.11 [11.27%]	19.03-31.56	18.58 [9.32%]	15.58-20.52
	60	38.81 [32.03%]	37.02-45.31	27.27[13.14%]	22.48-30.05
	80	48.93[6.92%]	42.38-53.46	55.12[12.23%]	43.55-59.39
	90			43.86[16.89%]	26.69-50.42
	100			46.12[9.00%]	44.46-54.15
	120			54.20[10.00%]	41.18-60.48
4 to 6 [17.34- 23.81]	10	6.15 [10.63 %]	4.93-6.88	4.46 [13.57%]	3.41-5.65
	20	13.43 [8.8%]	10.5-15.56	8.75 [12.41%]	3.41-5.65
	40	24.27 [11.93%]	18.34-27.36	17.39[13.98%]	12.95-21.19
	60	37.14 [10.57%]	25-56-39.51	27.15[9.92%]	21.51-30.06
	80	55.94 [11.11%]	39.37-56.82	32.86[14.18%]	20.93-37.34
	90			40.27[15.35%]	28.08-49.49
	100			44.98[9.91%]	34.79-49.15
	120			46.54[22.15%]	33.27-69.29
7 to 9 [26.54- 34.45]	10	7.35[9.96%]	6.02-8.51	4.74[14.46%]	4.50-5.68
	20	14.63[11.56%]	14.15-16.45	8.72[11.49%]	6.59-10.55
	40	26.46[14.98%]	18.33-30.52	18.19[11.24%]	14.64-21.36
	60	40.07[9.52%]	33.14-47.63	29.53[14.02%]	18.21-33.72
	80	53.75[13.29%]	35.48-61.83	37.40[9.99%]	28.52-42.19
	90			43.12[11.41%]	34.16-49.32
	100			45.56[13.04%]	32.35-52.23
	120			48.53[10.05%]	39.2-68.37
10 to 12 [38.9- 47.68]	10	7.35[9.96%]	6.02-8.51	5.42[14.74%]	5.05-6.19
	20	14.63[11.71%]	11.56-16.45	10.56[9.64%]	8.89-12.28
	40	29.37[10.04%]	22.40-33.36	16.42[13.89%]	11.84-19.6
	60	44.09[12.08%]	33.52-53.78	35.52[12.5%]	30.38-36.46
	80	58.05[7.97%]	50.39-67.97	42.15[13.09%]	30.03-44.75
	90			49.03[11.41%]	36.55-55.71
	100			54.41[16.92%]	35.92-67.54
	120			64.88[9.35%]	46.56-68.32

BID: twice a day; TID: three times a day

**Table 5.** Multivariate linear regression results for BID and TID regimen

Analysis	Results
R-square	0.924

<b>R-square Adjusted</b>	0.9236				
<b>Standard error</b>	4.92				
<b>Number of observations</b>	704				
ANOVA					
	<b>GL</b>	<b>SQ</b>	<b>MQ</b>	<b>F</b>	<b>p-value</b>
<b>Regression</b>	3	205924.9	68641.65	2837.26	<2 E-16
<b>Residual</b>	700	16935.04	24.19		
<b>Total</b>	703	222860			
	<b>Coefficients</b>	<b>Standard error</b>	<b>p-value</b>		
<b>Intersection (<math>\beta_0</math>)</b>	11.15501	0.78297	<2 E-16		
<b>Dose (<math>\beta_1</math>)</b>	0.48535	0.00532	<2 E-16		
<b>Weight (<math>\beta_2</math>)</b>	0.14558	0.01557	<2 E-16		
<b>Regimen (<math>\beta_3</math>)</b>					
<b>1 for BID and 2 for TID</b>	-8.52575	0.38399	<2 E-16		