

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Absorption:

Pharmacokinetics parameters of lacosamide following oral administration to mice.

Dose [mg/kg]	Duration	C _{max} [µg/mL]		T _{max} [h]		AUC ₀₋₂₄ [µg/mL]	
		Male	Female	Male	Female	Male	Female
20	Single dose	10.3	-	0.5 ^a	-	32.6	-
	1 day	13.5	10.1	1	0.5 ^a	33.4	28.3
	14 days	15.6	12.8	0.5 ^a	0.5 ^a	35.9	29.2
	6 months	12.6	11.8	0.5 ^a	0.5 ^a	36.3	27.8
	1 year	16.4	16.4	0.5 ^a	0.5 ^a	47.8	40.2
	2 years	12.6	10.5	0.5 ^a	0.5 ^a	28.9	33.5
30	1 day	16.0	18.8	1.0	0.5 ^a	60.5	48.4
		17.7	16.9	0.5 ^a	0.5 ^a	47.9	58.8
	14 days	16.8	14.0	0.5 ^a	0.5 ^a	45.8	39.5
	3 months	20.0	20.4	0.5 ^a	0.5 ^a	51.5	46.2
60	1 day	32.6	16.6	1	0.5 ^a	127	70.8
		26.9	24.7	0.5 ^a	0.5 ^a	95.1	96.5
	14 days	41.6	29.5	0.5 ^a	0.5 ^a	123	81.4
	3 months	29.0	27.6	0.5 ^a	0.5 ^a	97.0	131
	6 months	29.9	29.0	0.5 ^a	1	103	86.3
	1 year	33.9	37.0	0.5 ^a	0.5 ^a	103	95.3
	2 years	29.8	30.4	0.5 ^a	0.5 ^a	99.0	92.9
90	1 day	38.3	39.9	0.5 ^a	0.5 ^a	140	151
	14 days	24.8	30.1	0.5 ^a	0.5 ^a	154	91.3
120	1 day	40.5	46.3	1	0.5 ^a	189	205
	3 months	42.4	36.6	0.5 ^a	0.5 ^a	229	170
180	Single dose	61.5	-	0.5 ^a	-	250	-
	1 day	46.7	38.9	0.5 ^a	2	258	224
		56.1	81.5	1	1	269	362
	14 days	103	32.9	0.5 ^a	0.5 ^a	244	239
	3 months	53.8	45.9	0.5 ^a	0.5 ^a	315	240
	6 months	54.4	44.7	0.5 ^a	0.5 ^a	269	225
	1 year	78.8	44.7	0.5 ^a	1	306	193
	2 years	78.5	62.5	0.5 ^a	0.5 ^a	230	233
270	1 day	140	76.0	0.5 ^a	1	329	382
	14 days	53.6	40.7	1	2	458	283

Individual data or medians from 2 profiles are shown.

a - first sampling time

Data sources: Table 2.6.5.3B, — 1844704; Table 2.6.5.3C, — 18772/05; Table 2.6.7.3;

4.23.2.1 — 13122/00, Appendix 9-3; 4.23.2.2, — 13123/00, Appendix 10-5;

4.23.4.1.1, — 13124/00, Appendix 11-5.

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Pharmacokinetics parameters of lacosamide following oral administration to rats.

Dose [mg/kg]	Duration	C _{max} [µg/mL]		T _{max} [h]		AUC _{0-∞} [hrµg/mL]	
		Male	Female	Male	Female	Male	Female
30	1 day	10.7	13.0	0.5 ^a	1	62.4	78.3
		12.9	14.0	1	1	106	119
	3 months	12.0	14.4	1	1	61.3	80.8
		11.6	13.7	2	0.5 ^a	121	134
	6 months	11.2	12.4	1	1	140	131
40	6 months	17.6	27.5	0.5 ^a	0.5 ^a	169	185
	1 year	20.8	22.2	0.5 ^a	0.5 ^a	177	190
	2 years	15.2	17.9	0.5 ^a	0.5 ^a	180	202
80	6 months	27.6	34.4	0.5 ^a	1	299	429
	1 year	34.8	46.6	1	1	333	371
	2 years	27.1	29.3	0.5 ^a	0.5 ^a	373	342
90	1 day	23.6	25.3	1	2	262	311
	3 months	27.9	26.4	0.5 ^a	1	275	310
	6 months	21.8	33.7	4	1	296	339
100	1 day	21.8	22.0	0.5 ^a	1	147	152
	3 months	27.0	36.0	2	1	172	229
160	6 months	48.9	57.0	2	0.5 ^a	514	659
	1 year	57.9	-	2	-	512	-
	2 years	49.5	-	1	-	605	-
180	1 day	32.7	30.7	1	0.5 ^a	400	481
	3 months	38.2	33.9	2	1	539	501
	6 months	47.0	62.4	0.5 ^a	1	488	570
	1 year	-	59.6	-	1	-	687
200	2 years	-	51.6	-	0.5 ^a	-	737
300	1 day	34.2	40.3	1	2	218	216
	3 months	57.6	57.1	1	1	340	408

Values are medians or means (n = 2 to 3 profiles) or pharmacokinetic parameters were calculated with mean plasma concentrations.
^a - first sampling time
 Data sources: 4.2.3.2.5, 148-235, Pharmacokinetic evaluation report; 4.2.3.2.6 — 3227/00, Appendix 10-5; 4.2.3.4.1.2 — 3295/00, Appendix 11-5.

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Pharmacokinetics parameters of lacosamide following oral administration to adult dogs.

Dose [mg/kg]	Duration	C _{max} [µg/mL]		T _{max} [h]		AUC _{0-∞} [µg/mL]	
		Male	Female	Male	Female	Male	Female
5	1 day	7.35	6.11	1	1.5	18.4	21.0
	3 months	7.13	6.60	1	1	22.8	23.0
	9 months	5.79	5.40	1.5	1.3	19.8	21.0
	1 year	7.07	7.36	0.5	1.3	31.4	24.5
6	1 day	6.75	7.60	1 (0.5-1)	0.5 (0.25 ^a -1)	19.7	22.9
		9.11	8.60	0.8 (0.5-1)	0.8 (0.5-1)	20.9	21.7
	3 weeks	7.36	7.37	0.8 (0.5-1)	1 (0.5-1)	21.0	23.2
	3 months	9.47	6.24	0.5 (0.25 ^a -1)	1 (0.5-2)	27.1	19.4
10	1 day	12.1	9.97	1.3	1.3	43.8	35.5
	3 months	13.4	14.6	0.5	1.5	43.7	58.1
	9 months	14.5	12.7	0.5	1	74.1	49.8
	1 year	15.5	13.2	0.8	1.3	71.0	54.6
12	1 day	12.7	10.8	0.8 (0.5-2)	1.5 (0.5-2)	46.1	44.5
		16.7	15.3	0.5 (0.25 ^a -1)	0.6 (0.25 ^a -1)	31.6	29.8
	3 weeks	13.4	14.9	1 (0.5-2)	1 (0.5-1)	48.4	51.8
	3 months	17.0	15.6	0.5 (0.5-0.5)	1.5 (0.5-2)	49.0	45.5
12 (bid)	1 day	13.9±1.6	-	0.5 ^a (0.5 ^a -1)	-	42.1±6.1	-
	8 days	13.6±1.6	-	1 (0.5 ^a -2)	-	43.5±10.1	-
16 (bid)	1 day	18.1±2.7	-	1 (1-2)	-	69.8±8.0	-
	8 days	16.7±1.8	-	1 (1-1)	-	61.8±14.3	-
24	1 day	23.5	23.5	0.8 (0.25 ^a -2)	1 (0.5-2)	83.1	79.5
		27.1	27.4	1 (0.5-2)	1 (0.25 ^a -1)	65.2	59.4
	3 weeks	20.7	28.6	3 (1-4)	1 (0.5-2)	82.7	107
	3 months	32.8	27.6	0.5 (0.25 ^a -1)	0.8 (0.25 ^a -1)	102	85.2
25	1 day	23.1	17.1	1	1.5	95.6	68.6
	3 months	26.7	25.3	1.5	2	124	129
	9 months	29.9	27.4	1	1.5	166	133
	1 year	23.9	18.9	1.3	1	142	124

Values are means (± SD) (n=2, 4 or 5) except for T_{max} (median (range)). AUC_{0-∞} was determined over one dose interval.

a - first sampling time

bid = twice daily (12 hours apart)

Data sources: Table 2.6.5.31, 5654.02; 4.2.3.2.10, 98825 Pharmacokinetic evaluation report; 4.2.3.2.11, 98865, Toxicokinetic evaluation report; 4.2.3.2.12, 196.00, Appendix 10-5.

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Comparative pharmacokinetic data and systemic exposure to lacosamide following intravenous administration of lacosamide to dogs and human volunteers.

Species Route	Sex	Dose [mg/kg/day]	Parameter [unit]		
			C _{max} [µg/mL]	T _{1/2} [h]	AUC _{0-∞} [hrµg/mL]
Dog intravenous (bolus)	Male	4	6.7 ± 1.0	1.9 ± 0.3	25.3 ± 7
		8 (NOEL)	13.0 ± 0.5	1.7 ± 0.2	45.9 ± 4
		16	26.1 ± 1.4	2.1 ± 0.1	106 ± 4
	Female	4	6.4 ± 0.6	1.6 ± 0.3	22.3 ± 5
		8 (NOEL)	15.3 ± 1.8	1.7 ± 0.2	33.7 ± 7
		16	25.4 ± 1.2	1.7 ± 0.1	93.9 ± 7
Man intravenous (10 minutes)	Male	0.7 ^a	1.4 ± 0.6	13.5 ± 1.5	20.3 ± 2.5
		1.4 ^a	3.8 ± 1.3	12.2 ± 2.6	44.3 ± 6.6
		2.1 ^a	5.8 ± 1.9	12.3 ± 2.3	62.3 ± 13
		4.3 ^a	11.8 ± 2.5	12.3 ± 0.8	111 ± 12

Data presented are after repeated intravenous bolus injection at the end of a 14-day dog study (mean ± SD, n=4 per sex) or after single 10-minute intravenous infusion to healthy young male volunteers (mean ± SD, n=5 to 6).
^a - In man a body weight of 70 kg was assumed (50, 100, 150, 300 mg per subject).
 Data sources: 4.2.3.2.14, 98795, Pharmacokinetic evaluation report; 5.3.3.1.5, SP834, Table 14.2.1.

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Comparative pharmacokinetic data following repeated oral administration of lacosamide to mice, rats, dogs and human volunteers.

Species Route	Sex	Dose [mg/kg/day]	Parameter of lacosamide [unit]		
			C _{max} [µg/mL]	T _{max} [h]	AUC ₀₋₁₂ [hrµg/mL]
Mouse Oral (solution)	Male	30	20.0	0.5	51.5
		60 (NOAEL)	29.0	0.5	97.0
		120	42.4	0.5	229
		180	53.8	0.5	315
	Female	30	20.4	0.5	46.2
		60 (NOAEL)	27.6	0.5	131
		120	36.6	0.5	170
		180	45.9	0.5	240
Rat Oral (solution)	Male	30	11.2	1	140
		90 (NOAEL)	21.8	4	296
		180	47.0	0.5	488
	Female	30	12.4	1	131
		90 (NOAEL)	33.7	1	339
		180	62.4	1	570
Dog Oral (capsule)	Male	5	7.1	0.5	31.4
		10 (NOAEL)	15.5	0.8	71.0
		25	23.9	1.3	142
	Female	5	7.4	1.3	24.5
		10 (NOAEL)	13.2	1.3	54.6
		25	18.9	1.0	124
Man Oral (capsule)	Male	8.6 Day 15 (night)	12.6 ± 2.2	3 (1 - 6)	119 ± 18.3
		Day 16 (day)	14.5 ± 1.7	1 (1 - 2)	126 ± 17.4

Data presented are after repeated oral administration at the end of a 3-month mouse (individual data), 6-month rat (median, n=3), 12-month dog (median, n=2) and 16-day human trial SP588 (means ± SD, n=12, T_{max} median (range)). In man a body weight of 70 kg was assumed (2 x 300 mg per subject/day).

AUC₀₋₁₂ in the mouse, rat and dog, and AUC₀₋₁₂ in man are given.
 Data sources: 4.2.3.2.2. — 13125/00, Appendix 10-5, 4.2.3.2.6. — 3227/00, Appendix 10-5, 4.2.3.2.12.
 — 13196/00, Appendix 10-5, 5.3.3.1.4, SP588, Section 9.4.

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