Table 3. Descriptive statistics for total phenytoin concentrations (µg/mL) in plasma over time

Day	Time postdose (h)	Total time from first dose (h)	N	Mean	SD	Min	Median	Max	CV%
1	0	0	11	0.00	0.00		0.00		0.00
10	0	216	11	8.75	4.11		9.58		47.01
11	0	240	11	9.07	3.02		9.05		33.35
12	0	264	11	9.77	3.00		10.40		30.68
12	0.5	264.5	11	9.64	2.83		9.99		29.36
12	1	265	11	9.46	3.49		9.69		36.86
12	2	266	11	9.65	3.29		10.40		34.03
12	3	267	11	10.17	3.09		9.90		30.39
12	4	268	11	9.23	3.04		8.80		32.96
12	6	270	11	9.65	2.75		9.18		28.51
12	8	272	11	9.13	2.92		8.77		32.02
12	10	274	11	10.10	2.87		10.20		28.46
12	12	276	11	8.97	2.61		8.98		29.04
18	0	408	10	9.74	4.02		9.68		41.29
21	0	480	10	8.95	4.36		8.19		48.68
22	0	504	10	9.42	4.43		8.50		47.07
23	0	528	10	8.20	4.65		7.96		56.68
30	0	696	10	8.68	4.29		7.82		49.39
37	0	864	10	9.97	5.59		8.97		56.09
42	0	984	10	9.03	5.30		6.87		58.73
43	0	1008	10	9.28	6.20		6.84		66.83
44	0	1032	10	9.19	6.70		6.25		72.91
44	0.5	1032.5	10	9.08	6.32		6.68		69.63
44	1	1033	10	9.54	6.63		6.81		69.54
44	2	1034	10	9.84	6.41		7.29		65.16
44	3	1035	10	9.51	5.88		7.28		61.80
44	4	1036	10	9.56	6.24		7.02		65.28
44	6	1038	10	8.77	6.27		6.50		71.51
44	8	1040	10	9.42	6.74		6.54		71.49

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Day	Time postdose (h)	Total time from first dose (h)	N	Mean	SD	Min	Median	Max	CV%
44	10	1042	10	8.86	6.35		6.13		71.75
44	12	1044	10	8.89	6.16		5.99		70.90
44	24	1056	6	11.02	7.35		9.35		66.69
44	48	1080	6	9.24	5.96		7.97		64.52
51	0	1200	4	7.53	3.29		7.34		43.70
59	9	1368	4	8.23	2.49		5.87		39.97
63	0	1488	4	5.51	1.89		5.32		34.39
64	0	1512	4	5.52	2.46		5.05		44.66
65	0	1536	4	5.67	2.74		4.79		48.28
65	0.5	1536.5	4	5.73	2.76		5.00		48.17
65	1	1537	4	6.05	2.71		5.39		44.88
65	2	1538	4	6.13	2.22		5.70		36.13
65	3	1539	4	5.93	2.20		5.17		37.17
65	4	1540	4	6.01	2.01		5.51		33.46
65	6	1542	4	5.80	2.08		5.33		35.81
65	8	1544	4	5.57	1.96		5.03		35.20
65	10	1546	4	5.52	2.09		4.92		37.86
65	12	1548	4	5.03	1.93		4.48		38.45
65	24	1560	4	5.45	2.08		4.79		38.14
65	48	1584	4	4.06	1.83		3.50		45.14

Supporting data:
Appendix C.2.2.1 Listing of plasma concentration over time for total phenytoin page 741

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Table 4. Descriptive statistics for phenytoin 5pHPPH metabolite concentrations (µg/mL) in plasma over time

Day	Time postdose (h)	Total time from first dose (h)	N	Mean	SD	Min	Median	Max	%CV
1	0	0	4	0.00	0.00		0.00		0.00
10	0	216	4	0.19	0.04		0.20		22.33
11	0	240	4	0.18	0.04		0.17		23.57
12	0	264	4	0.18	0.04		0.17		23.09
12	0.5	264.5	4	0.21	0.05		0.21		22.04
12	1	265	4	0.20	0.03		0.20		13.57
12	2	266	4	0.20	0.02		0.19		11.23
12	3	267	4	0.19	0.04		0.20		20.06
12	4	268	4	0.19	0.02		0.20		11.37
12	6	270	4	0.20	0.02		0.20		11.23
12	8	272	4	0.19	0.05		0.19		24.00
12	10	274	4	0.20	0.03		0.19		17.52
12	12	276	4	0.19	0.04		0.18		18.73
18	0	408	4	0.15	0.12		0.16		79.44
21	0	480	4	0.19	0.06		0.21		30.08
22	0	504	4	0.18	0.07		0.18		40.20
23	0	528	4	0.14	0.11		0.16		76.53
30	0	696	4	0.12	0.09		0.15		70.66
37	0	864	4	0.14	0.10		0.16		72.82
42	0	984	4	0.12	0.08		0.15		68.04
43	0	1008	4	0.13	0.09		0.17		68.45
44	0	1032	4	0.18	0.07		0.17		41.57
44	0.5	1032.5	4	0.17	0.05		0.17		30.30
44	1	1033	4	0.17	0.05		0.18		27.33
44	2	1034	4	0.15	0.03		0.16		23.07
44	3	1035	4	0.15	0.03		0.16		17.83
44	4	1036	4	0.15	0.03		0.15		18.25
44	6	1038	4	0.12	0.08		0.15		67.15
44	8	1040	4	0.14	0.02		0.15		16.58

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Day	Time postdose (h)	Total time from first dose (h)	N	Mean	SD	Min	Median	Max	%CV
44	10	1042	4	0.14	0.02		0.15		17.50
44	12	1044	4	0.14	0.02		0.15		15.58
45	0	1056	2	0.15	0.02		0.15		14.63
48	0	1080	2	0.14	0.03		0.14		20.20
51	0	1200	2	0.55	0.47		0.55		86.93
58	0	1368	2	0.18	0.04		0.18		23.57
63	0	1488	2	0.17	0.02		0.17		12.86
64	0	1512	2	0.18	0.01		0.18		7.86
65	0	1536	2	0.18	0.04		0.18		23.57
65	0.5	1536.5	2	0.18	0.06		0.18		31.43
65	1	1537	2	0.17	0.04		0.17		24.96
65	2	1538	2	0.17	0.04		0.17		24.96
65	3	1539	2	0.18	0.03		0.18		15.71
65	4	1540	2	0.17	0.00		0.17		0.00
65	6	1542	2	0.17	0.01		0.17		8.32
65	8	1544	2	0.16	0.01		0.16		8.84
65	10	1546	2	0.17	0.05		0.17		30.00
65	12	1548	2	0.17	0.02		0.17		12.86
65	24	1560	2	0.16	0.03		0.16		17.68
65	48	1584	2	0.13	0.03		0.13		21.76

Supporting data:
Appendix C.2.2.2 Listings of plasma concentration over time for 5pHPPH phenytoin metabolite page 746

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Table 5. Descriptive statistics for free phenytoin concentrations (µg/mL) in plasma over time

Day	Time postdose (h)	Time from first dose (h)	N	Mean	SD	Min	Median	Max	CV%
1	0	0	11	0.00	0.00		0.00		0.00
12	0	264	11	1.46	0.49		1.34		33.33
12	1	265	11	1.46	0.45		1.31		31.06
12	12	276	11	1.35	0.47		1.19		34.49
18	0	408	10	1.48	0.59		1.25		39.54
23	0	528	10	1.38	0.58		1.21		42.08
30	0	696	10	1.35	0.64		1.17		47.51
37	0	864	10	1.35	0.75		1.18		55.33
44	0	1032	10	1.37	0.91		0.99		66.21
44	1	1033	10	1.40	0.90		0.98		63.80
44	12	1044	10	1.29	0.94		0.88		73.19
45	0	1056	6	1.60	1.01		1.33		63.24
46	0	1080	6	1.42	1.00		1.13		70.57
51	0	1200	4	0.75	0.14		0.76		18.19
58	0	1368	4	1.24	0.24		1.19		19.45
65	0	1536	4	0.88	0.34		0.80		38.33
65	1	1537	4	0.97	0.33		0.88		33.99
65	12	1548	4	0.78	0.27		0.69		35.02

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Table 6. Descriptive statistics for vigabatrin concentrations (µg/mL) in plasma over time

Day	Time postdose (h)	Total time from first dose (h)	N	Mean	SD	Min	Median	Max	CV%	Dose adjusted mean*	Pooled days	Mean pooled across days	CV% for pooled mean
12	0	264	11	0.00	0.00		0.00		0.00	0.00	-	-	-
21	0	480	10	4.47	0.84		4.66		18.82	6.71	21-23	6.59*	17.53
22	0	504	10	4.36	0.79		4.41		18.15	6.55	-	-	-
23	0	528	10	4.34	0.75		4.45		17.31	6.51	-	-	-
42	0	984	10	5.96	1.12		5.71		18.85	-	42-44	5.90	18.17
43	0	1008	10	5.77	0.98		6.08		17.06	-	-	-	-
44	0	1032	10	5.97	1.20		5.98		20.14	-	-	-	-
63	0	1488	4	5.50	1.52		5.37		27.66	-	63-65	5.48	23.98
64	0	1512	4	5.73	1.33		5.85		23.14	-	-	-	-
65	0	1536	4	5.19	1.43		4.92		27.57	-	-	-	-

*dose adjusted from 1.0 g to 1.5 g

Supporting data:
Appendix C.2.2.4 Listings of plasma concentration over time for vigabatrin page 754

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Table 7. Descriptive statistics for total phenytoin plasma pharmacokinetic parameters

Day	Statistic	$T_{max,ss}$	$C_{max,ss}$	$C_{min,ss}$	$AUC(0\text{-}12)_{,ss}$	lambda z	$t_{1/2}$	$Cl_{po,ss}$
		h	µg/mL	µg/mL	h•µg/mL	1/h	h	mL/min
day 12	mean	3.41	10.94	8.97	114.75	.	.	23.59
	sd	2.96	3.04	2.61	33.34	.	.	7.05
	%CV	86.72	27.79	29.04	29.05	.	.	29.89
	median	3.00	11.90	8.98	110.16	.	.	22.69
	N	11.00	11.00	11.00	11.00	.	.	11.00
day 44	mean	3.70	10.01	7.63	110.46	0.0054	133.27	30.44
	sd	2.41	6.70	4.97	76.15	0.0013	30.61	14.08
	%CV	65.03	66.89	65.15	68.94	24.4026	22.97	46.24
	median	2.59	7.29	5.48	80.04	0.0052	134.92	31.44
	N	10.00	10.00	10.00	10.00	6.0000	6.00	10.00

Supporting data:
Appendix C.2.2.12 Plasma individual pharmacokinetic parameters for total phenytoin page 813

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Table 18. Descriptive statistics for total phenytoin urine pharmacokinetic parameters

		Urine Volume	*Amount Excreted in Urine*	*% Dose Excreted in Urine*	*Renal Clearance*
		mL	mcg	%	mL/min
day 12	mean	1017.20	1407.33	0.94	0.22
	sd	855.96	980.92	0.65	0.15
	%CV	84.15	69.70	69.70	68.76
	median	738.50	1248.50	0.83	0.17
	N	10.00	10.00	10.00	10.00
day 44	mean	735.40	1182.71	0.79	0.19
	sd	412.17	1064.35	0.71	0.12
	%CV	56.05	89.99	89.99	63.32
	median	583.50	770.69	0.51	0.13
	N	10.00	10.00	10.00	10.00
day 85	mean	1141.25	937.73	0.63	0.23
	sd	813.25	561.01	0.37	0.15
	%CV	71.26	59.83	59.83	63.66
	median	757.50	834.10	0.56	0.16
	N	4.00	4.00	4.00	4.00

Supporting data:
Appendix C.2.2.8 Urine pharmacokinetic parameters for total phenytoin page 801

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Table 11. Descriptive statistics for unconjugated 5pHPPH urine pharmacokinetic parameters

		Urine Volume	*Amount Excreted in Urine*	*% Dose Excreted in Urine*
		mL	*mcg*	*%*
day 12	mean	982.82	1143.79	0.72
	sd	820.00	645.69	0.40
	%CV	83.43	56.45	56.45
	median	639.00	1203.20	0.75
	N	11.00	11.00	11.00
day 44	mean	735.40	1149.74	0.72
	sd	412.17	583.94	0.37
	%CV	56.05	50.79	50.79
	median	583.50	1037.03	0.65
	N	10.00	10.00	10.00
day 65	mean	1141.25	1303.64	0.82
	sd	813.25	851.71	0.53
	%CV	71.26	65.33	65.33
	median	757.50	1040.75	0.65
	N	4.00	4.00	4.00

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Supporting data:
Appendix C.2.2.10 Urine pharmacokinetic parameters for unconjugated 5pHPPH phenytoin metabolite page 807

Table 12. Descriptive statistics for total 5pHPPH and conjugated 5pHPPH urine pharmacokinetic parameters

		Urine volume	*Amount of total 5pHPPH excreted in urine*	*% dose excreted in urine for total (conjugated + unconjugated) 5pHPPH*	*Amount of conjugated 5pHPPH excreted in urine*	*% dose excreted in urine for conjugated 5pHPPH*
		mL	*mcg*	*%*	*mcg*	*%*
day 12	mean	982.82	82098.22	31.36	80954.43	30.65
	sd	820.00	29765.29	11.00	28337.71	10.73
	%CV	83.43	35.04	35.06	35.00	35.00
	median	639.00	69102.00	26.52	67643.40	25.61
	N	11.00	11.00	11.00	11.00	11.00
day 44	mean	735.40	93006.24	35.50	91856.50	34.77
	sd	412.17	28640.72	10.93	28277.13	10.70
	%CV	56.05	30.79	30.81	30.78	30.78
	median	583.50	101358.90	38.69	99844.52	37.80
	N	10.00	10.00	10.00	10.00	10.00
day 65	mean	1141.25	83110.13	31.79	81806.49	30.97
	sd	813.25	16521.03	6.45	15721.85	5.95
	%CV	71.26	19.88	20.30	19.22	19.22
	median	757.50	75739.00	28.93	74698.25	28.28
	N	4.00	4.00	4.00	4.00	4.00

Supporting data:
Appendix C.2.2.11 Urine pharmacokinetic parameters for conjugated 5pHPPH phenytoin metabolite page 810
Appendix C.2.2.9 Urine pharmacokinetic parameters for total 5pHPPH phenytoin metabolite page 804

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Table 13. Trough analysis for total phenytoin, 5pHPPH, and vigabatrin to determine if concentrations are at steady-state

				Pairwise comparisons			
Analyte	*Treatment*	*Day*	*Adjusted mean*	*Pair (by day)*	*Pairwise ratio*	*90% CI*	*P-value*
Total phenytoin	phenytoin alone (day 10-12)	10	9.69	11/10	99.19	(89.8,109.5)	0.89
		11	9.62	12/10	104.94	(94.3,116.7)	0.444
		12	10.17	12/11	105.79	(95.1,117.7)	0.372
	day 42-44	42	6.83	43/42	98.31	(93.3,103.5)	0.576
		43	6.71	44/42	96.41	(91.5,101.5)	0.237
		44	6.58	44/43	98.07	(93.1,103.3)	0.523
5pHPPH	phenytoin alone (day 10-12)	10	0.18	11/10	88.54	(76.3,102.7)	0.167
		11	0.16	12/10	96.66	(81.2,115.1)	0.726
		12	0.18	12/11	109.16	(91.7,130.0)	0.377
	day 42-44	42	0.12	43/42	110.23	(91.8,132.3)	0.319
		43	0.13	44/42	125.99	(105.0,151.2)	0.054
		44	0.15	44/43	114.30	(95.2,137.2)	0.193
Vigabatrin	day 21-23	21	4.43	22/21	90.00	(77.5,104.5)	0.237
		22	3.98	23/21	93.51	(80.2,109.1)	0.462
		23	4.14	23/22	103.91	(89.1,121.2)	0.673
	day 42-44	42	6.04	43/42	97.13	(91.2,103.4)	0.434
		43	5.86	44/42	99.88	(93.8,106.4)	0.973
		44	6.03	44/43	102.83	(96.6,109.5)	0.454
	day 63-65	63	5.35	64/63	105.00	(96.8,113.9)	0.29
		64	5.61	65/63	94.53	(87.1,102.6)	0.229
		65	5.05	65/64	90.03	(83.0, 97.7)	0.047

phenytoin alone (day 10-12): days 10-12, phenytoin 150 mg Q12 h alone
day 42-44: days 42-44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h for 3 weeks
day 63-65: days 63-65, phenytoin 150 mg and vigabatrin 1.5 g Q12 h for 6 weeks

Supporting data:
Appendix B.3.13 Analysis of variance summary - total phenytoin trough plasma concentration page 368
Appendix B.3.18 Details of within treatment analysis – 5pHPPH trough plasma concentration page 378

Table 14. Individual percent change in plasma and urine pharmacokinetic parameters for total phenytoin and 5pHPPH after 3 weeks coadministration of vigabatrin andphenytoin versus phenytoin alone

	Total phenytoin in plasma			*Total phenytoin in urine*					*5pHPPH in urine*
Subject	*Cmax,ss*	*Cmin,ss*	*AUC(0-12 h),ss*	*Ae*	*Renal Clearance*	*Ae total*	*Ae conjugated*	*Ae unconjugated*	*Renal clearance total*
VGST1849-	*mcg/mL*	*mcg/mL*	*h*mcg/mL*	*mcg*	*mL/min*	*mcg*	*mcg*	*mcg*	*mL/min*

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percent change = [(day 44 - day 12)/day 12] x 100

Supporting data:

Appendix C.2.2.12 Plasma individual pharmacokinetic parameters for total phenytoin	page 813
Appendix C.2.2.8 Urine pharmacokinetic parameters for total phenytoin	page 801
Appendix C.2.2.11 Urine pharmacokinetic parameters for conjugated 5pHPPH phenytoin metabolite	page 810

Table 15. Incidence of All Adverse Events

ADVERSE EVENT SYSTEM ORGAN CLASS PREFERRED TERM	Phenytoin N=15		Vigabatrin Titrate Up N=14		Steady State Coadmin N=11		Titrate Down N=11	
	N	%	N	%	N	%	N	%
HEPATIC & BILIARY	0	0.0%	8	57.1%	2	18.2%	0	0.0%
GGT INCREASED	0	0.0%	8	57.1%	2	18.2%	0	0.0%
NEUROLOGIC	1	6.7%	3	21.4%	3	27.3%	0	0.0%
DIZZINESS	1	6.7%	0	0.0%	2	18.2%	0	0.0%
HEADACHE	1	6.7%	0	0.0%	1	9.1%	0	0.0%
SPEECH DISORDER	0	0.0%	1	7.1%	0	0.0%	0	0.0%
TREMOR	0	0.0%	1	7.1%	0	0.0%	0	0.0%
SOMNOLENCE	0	0.0%	1	7.1%	0	0.0%	0	0.0%
PSYCHIATRIC	3	20.0%	2	14.3%	1	9.1%	0	0.0%
INSOMNIA	2	13.3%	0	0.0%	0	0.0%	0	0.0%
AGGRESSIVE REACTION	0	0.0%	0	0.0%	1	9.1%	0	0.0%
AMNESIA	0	0.0%	0	0.0%	1	9.1%	0	0.0%
ANOREXIA	1	6.7%	0	0.0%	0	0.0%	0	0.0%
APPETITE INCREASED	0	0.0%	0	0.0%	1	9.1%	0	0.0%
CONFUSION	0	0.0%	1	7.1%	1	9.1%	0	0.0%
EMOTIONAL LABILITY	0	0.0%	0	0.0%	1	9.1%	0	0.0%
NERVOUSNESS	1	6.7%	1	7.1%	0	0.0%	0	0.0%
PARANOID PSYCHOSIS	0	0.0%	0	0.0%	1	9.1%	0	0.0%
DERMATOLOGIC	1	6.7%	0	0.0%	2	18.2%	0	0.0%
ACNE	0	0.0%	0	0.0%	2	18.2%	0	0.0%
RASH	1	6.7%	0	0.0%	1	9.1%	0	0.0%
GASTROINTESTINAL	1	6.7%	1	7.1%	1	9.1%	0	0.0%
VOMITING	1	6.7%	0	0.0%	1	9.1%	0	0.0%
FLATULENCE	0	0.0%	1	7.1%	0	0.0%	0	0.0%
NAUSEA	1	6.7%	0	0.0%	0	0.0%	0	0.0%
BODY AS A WHOLE - GENERAL	0	0.0%	2	14.3%	1	9.1%	0	0.0%
ABDOMINAL PAIN	0	0.0%	1	7.1%	0	0.0%	0	0.0%
BACK PAIN	0	0.0%	0	0.0%	1	9.1%	0	0.0%
FATIGUE	0	0.0%	1	7.1%	0	0.0%	0	0.0%
CARDIOVASCULAR	0	0.0%	0	0.0%	0	0.0%	1	9.1%
BRADYCARDIA	0	0.0%	0	0.0%	0	0.0%	1	9.1%
MUSCULOSKELETAL	0	0.0%	0	0.0%	0	0.0%	1	9.1%
ARTHRALGIA	0	0.0%	0	0.0%	0	0.0%	1	9.1%
RESPIRATORY	1	6.7%	0	0.0%	1	9.1%	0	0.0%
EPISTAXIS	0	0.0%	0	0.0%	1	9.1%	0	0.0%
PHARYNGITIS	1	6.7%	0	0.0%	0	0.0%	0	0.0%
PATIENTS WITH ONE OR MORE ADVERSE EVENTS	6	40.0%	9	64.3%	5	45.5%	2	18.2%

Phenytoin: Phenytoin 200 mg Q12h x 1 day followed by Phenytoin 150 mg Q12h
Vigabatrin Titrate Up: Phenytoin 150 mg Q12h + Vigabatrin 500 mg Q12h x 5 days and Phenytoin 150 mg Q12h + Vigabatrin 1 g Q12h x 5 days
Steady State Coadmin: Phenytoin 150 mg Q12h + Vigabatrin 1.5 g Q12h
Titrate Down: Phenytoin 100 mg Q12h + Vigabatrin 1 g Q12h x 1 day followed by Phenytoin 100 mg QAM + Vigabatrin 500 mg Q12h

Supporting data:
Appendix C.3.2.1.1 Adverse Event Mapping page 832
Appendix C.3.2.1.2 Adverse Events page 836

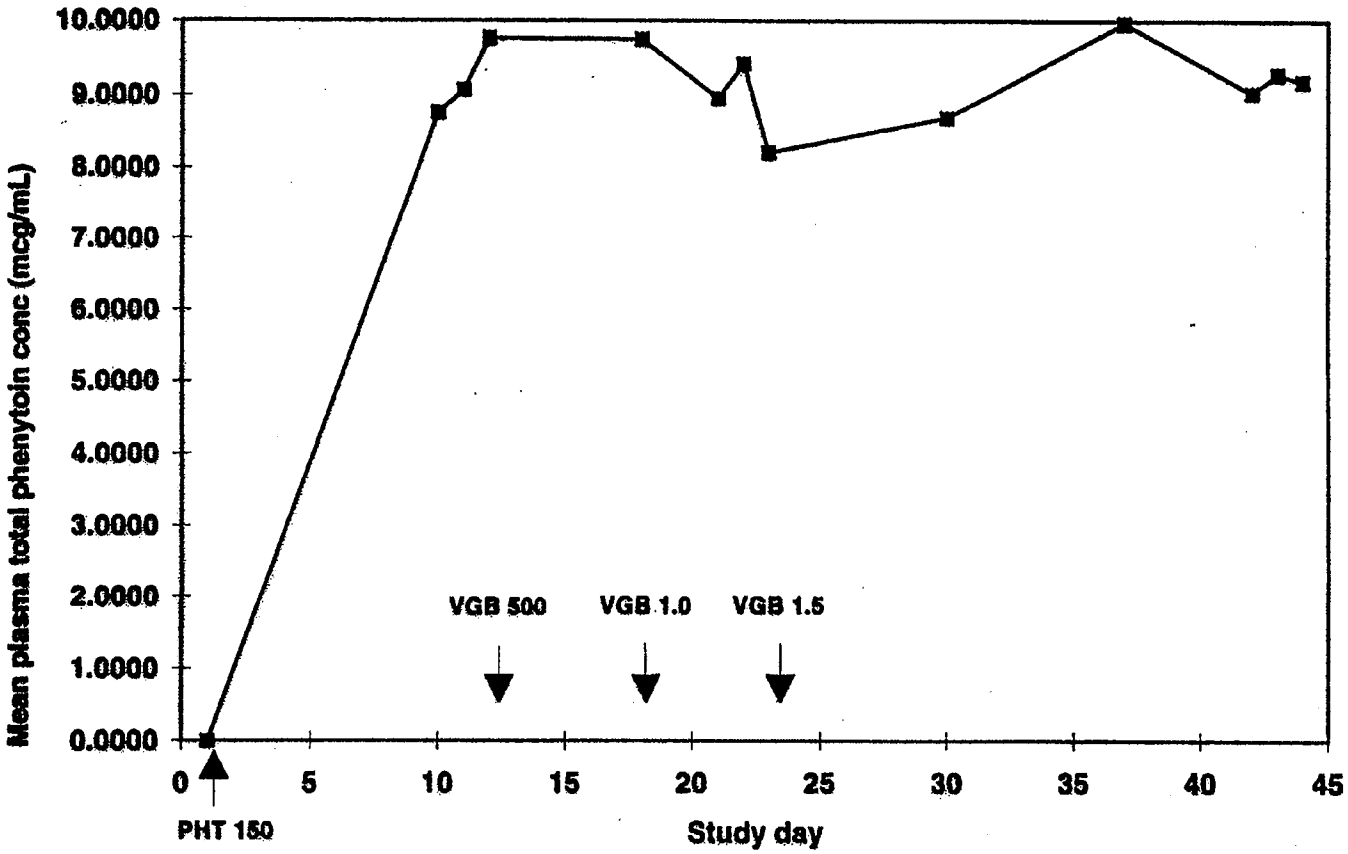


Figure 1. Mean total phenytoin trough plasma concentrations over time when phenytoin 150 mg was administered alone every 12 hours (PHT 150) and during titration up to and including coadministration with vigabatrin 1.5 grams every 12 hours (VGB 500 = vigabatrin 500 mg; VGB 1.0 = vigabatrin 1.0 g; and VGB 1.5 = vigabatrin 1.5 g)

Supporting data:

Table 1 Descriptive statistics for total phenytoin concentrations (µg/mL) in plasma over time

page 2

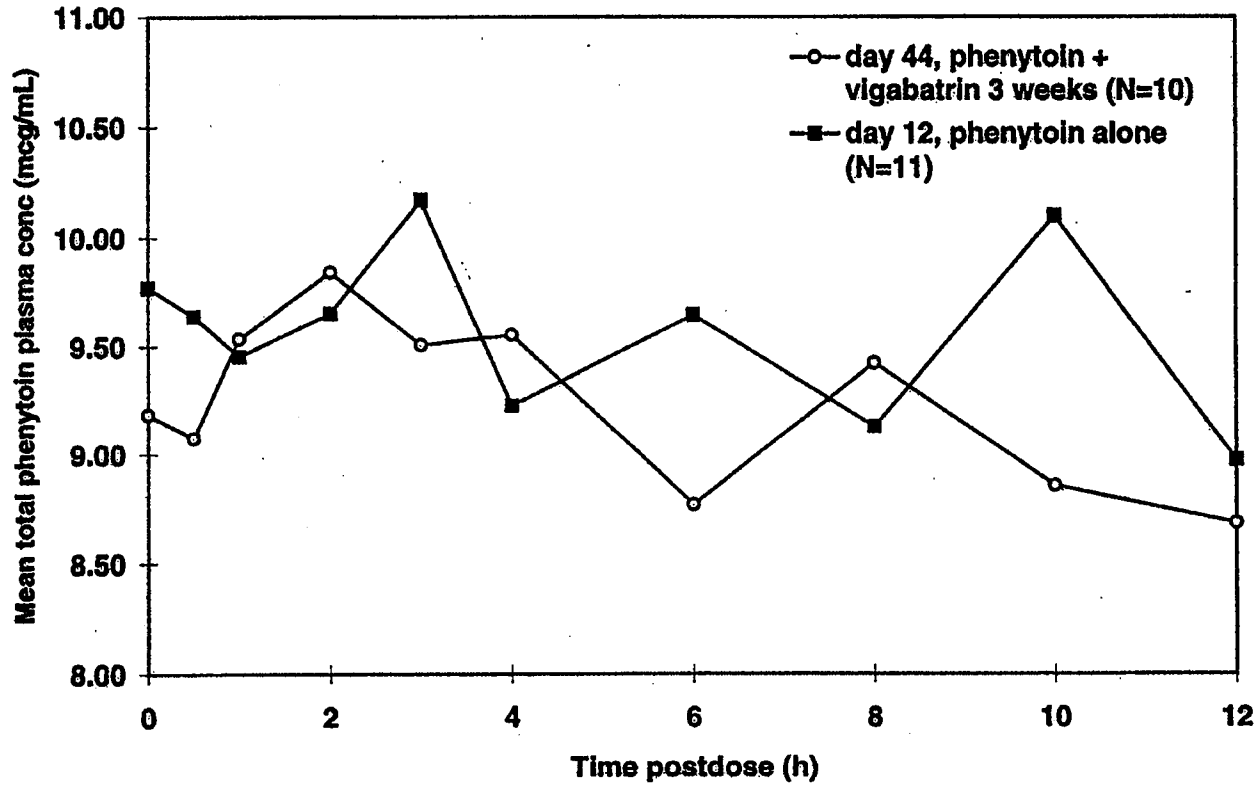


Figure 2. Mean plasma total phenytoin concentrations over the 12 hour dosing interval when phenytoin 150 mg was administered alone every 12 hours (day 12) compared to after 3 weeks (day 44) of coadministration with vigabatrin 1.5 grams every 12 hours.

Supporting data:

Table 3. Descriptive statistics for total phenytoin concentrations (µg/mL) in plasma over time *page 9*

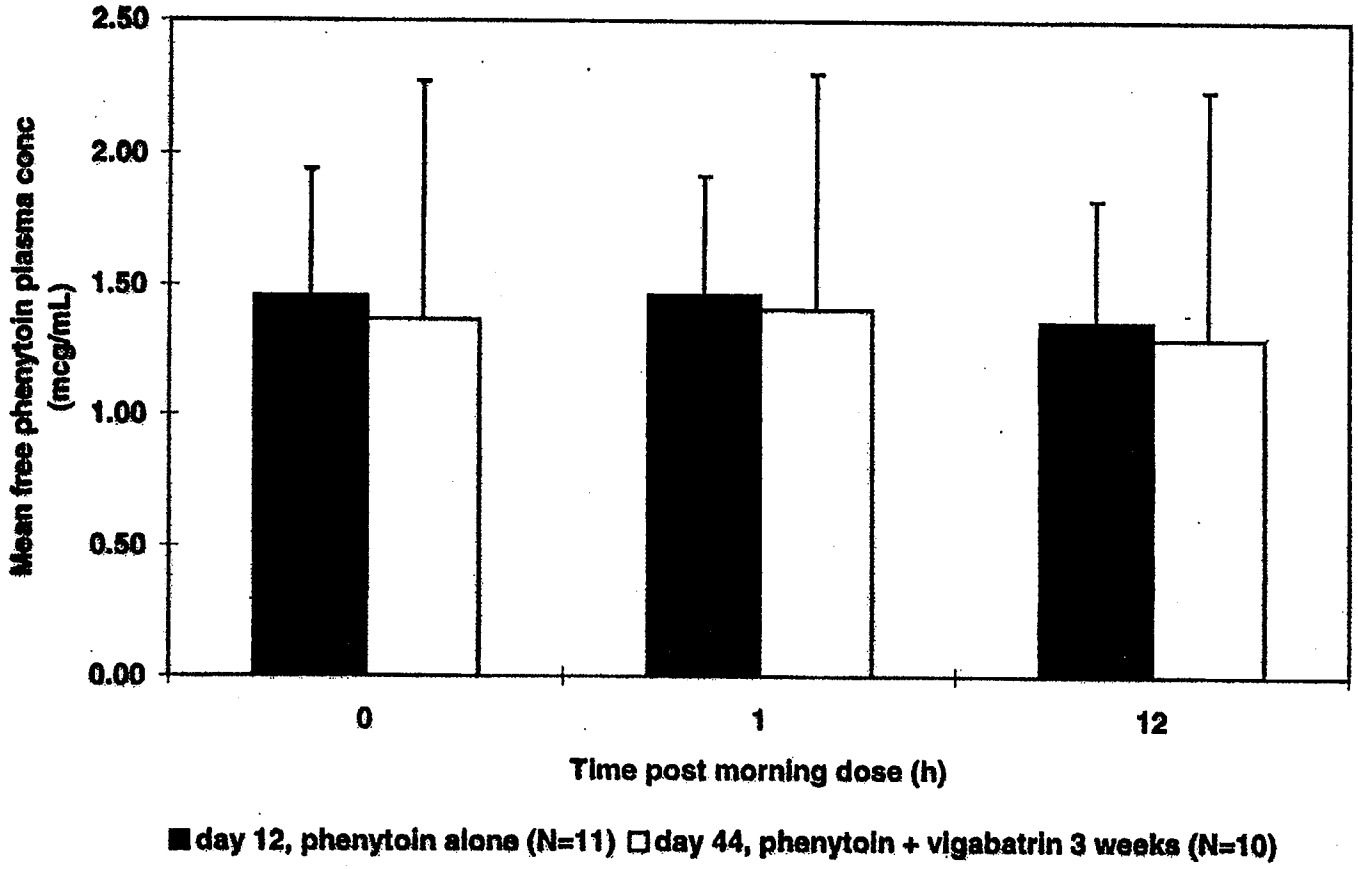


Figure 3. Mean (with standard deviation) free phenytoin plasma concentrations over the 12 hour dosing interval when phenytoin 150 mg was administered alone every 12 hours (day 12) compared to after 3 weeks (day 44) of coadministration with vigabatrin 1.5 grams every 12 hours.

Supporting data:

Table 5. Descriptive statistics for free phenytoin concentrations (µg/mL) in plasma over time

page 13

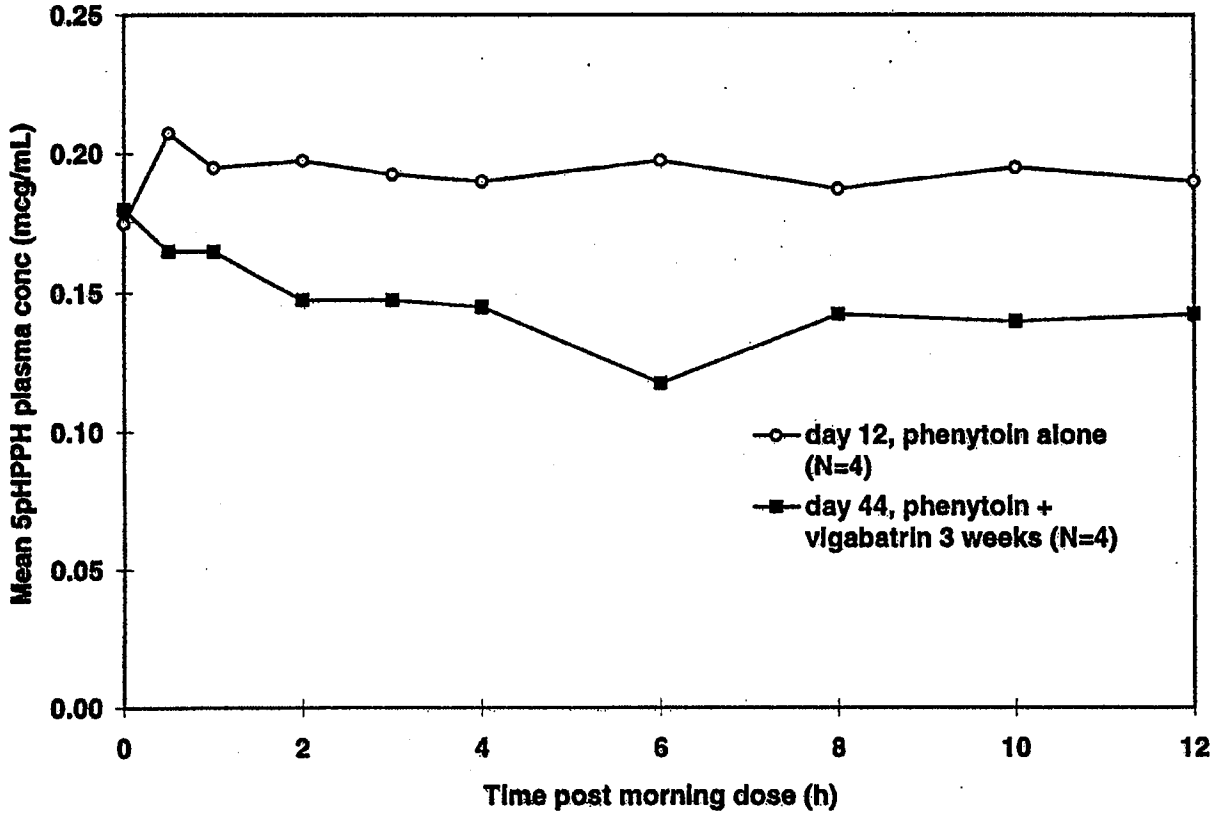
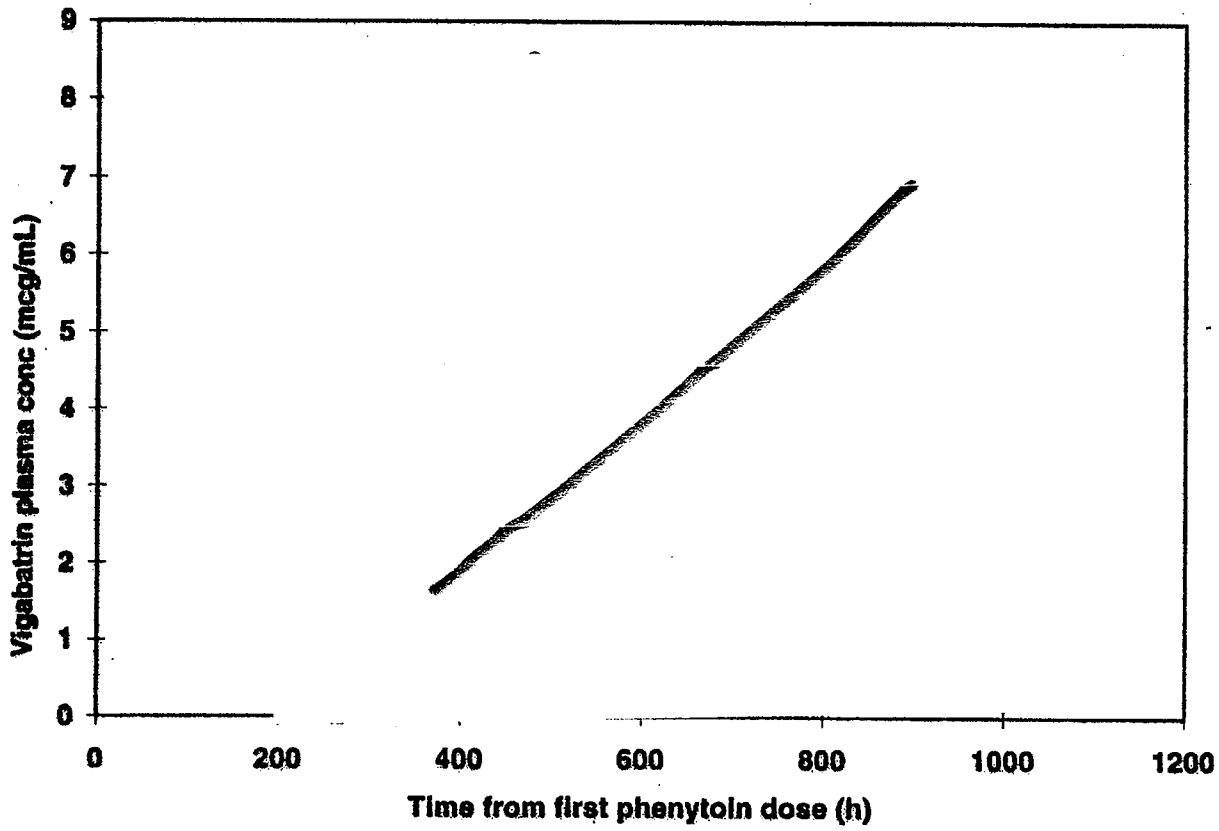


Figure 4. Mean of the 4 subjects with quantifiable phenytoin 5pHPPH metabolite plasma concentrations over the 12 hour dosing interval when phenytoin 150 mg was administered alone every 12 hours (day 12) compared to after 3 weeks (day 44) of coadministration with vigabatrin 1.5 grams every 12 hours.

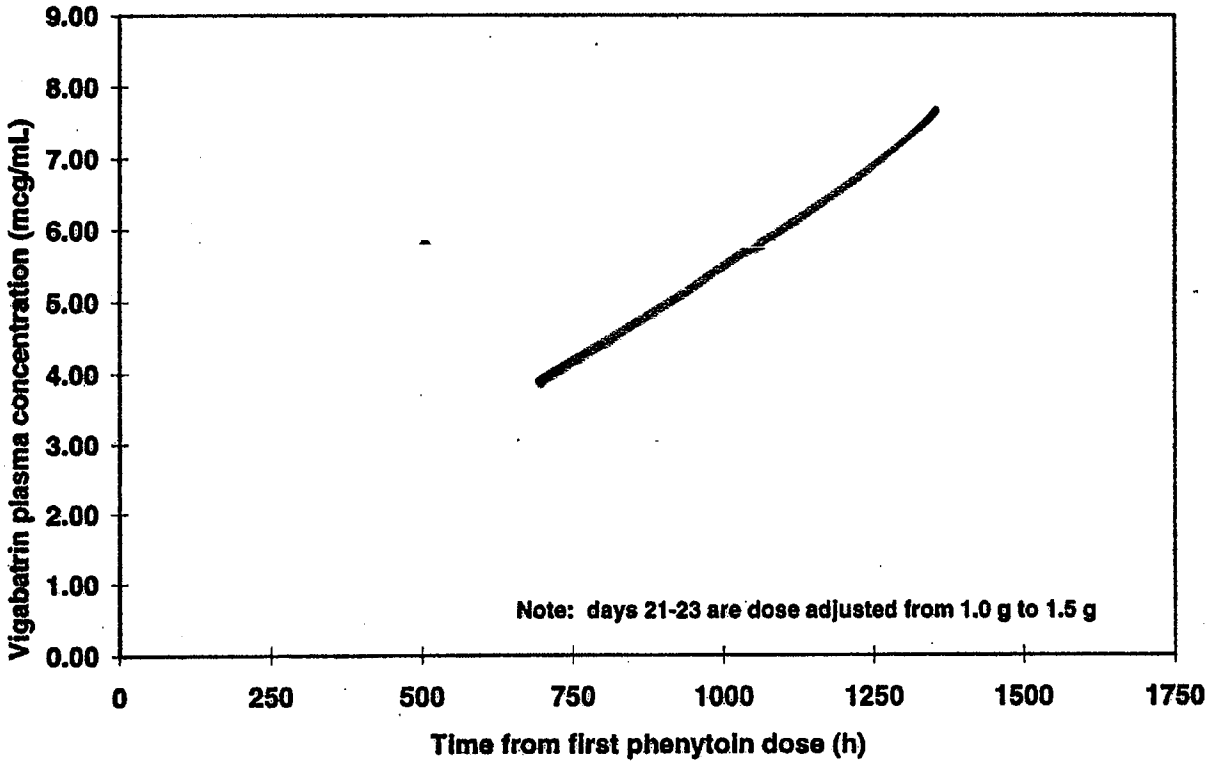
Supporting data:
Table 4. Descriptive statistics for phenytoin 5pHPPH metabolite concentrations (µg/mL) in plasma over time *page 11*



b(4)

Figure 6. Mean and individual vigabatrin trough plasma concentrations over time following vigabatrin 1.5 grams and phenytoin 150 mg every 12 hours at the start of the 3 week coadministration (days 21-23) and after coadministration for 3 weeks (days 42-44)

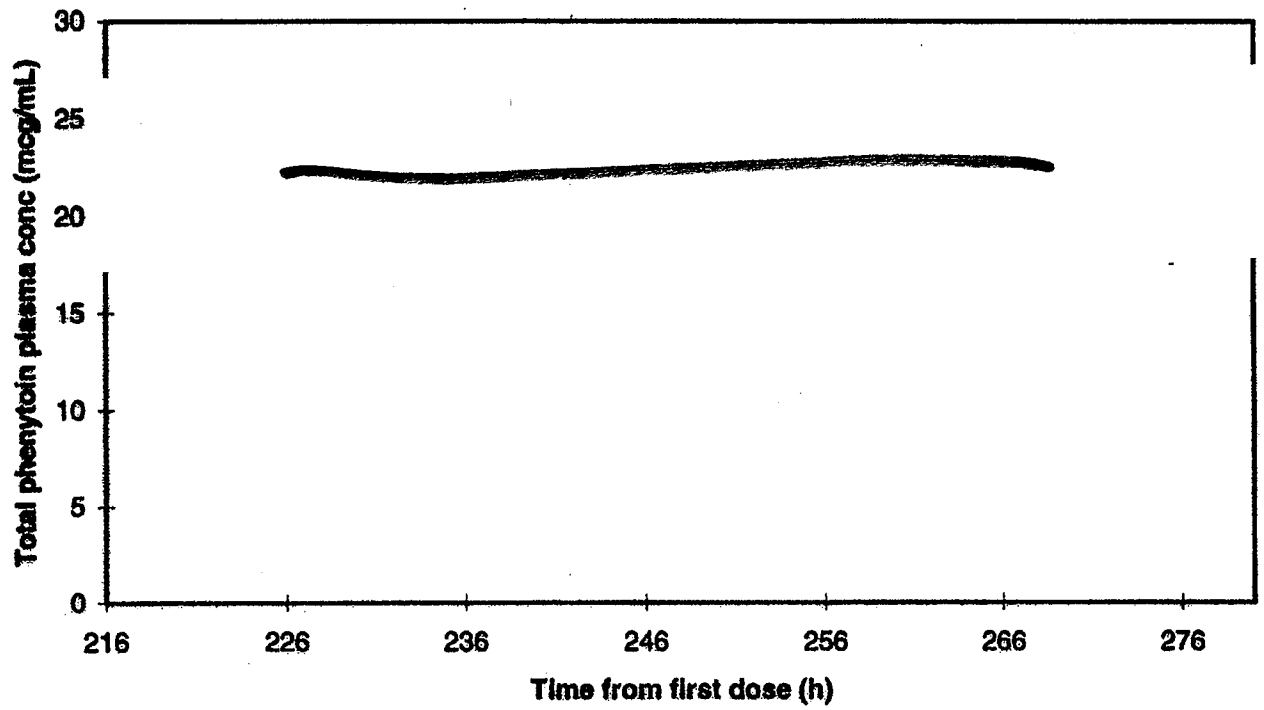
Supporting data:
Table 6. Descriptive statistics for vigabatrin concentrations (µg/mL) in plasma over time *page 14*
Appendix C.2.2.4 Listings of plasma concentration over time for vigabatrin *page 754*



b(4)

Figure 6. Individual vigabatrin trough plasma concentrations over time for subjects VGST1849-0001 to 0005 on days 21-23 while administering phenytoin 150 mg and a 5 day titration of vigabatrin 1.0 g every 12 hours (concentrations dose adjusted to 1.5 g vigabatrin) and after coadministration of phenytoin 150 mg and vigabatrin 1.5 g every 12 hours for 3 weeks (days 42-44) and 6 weeks (days 63-65)

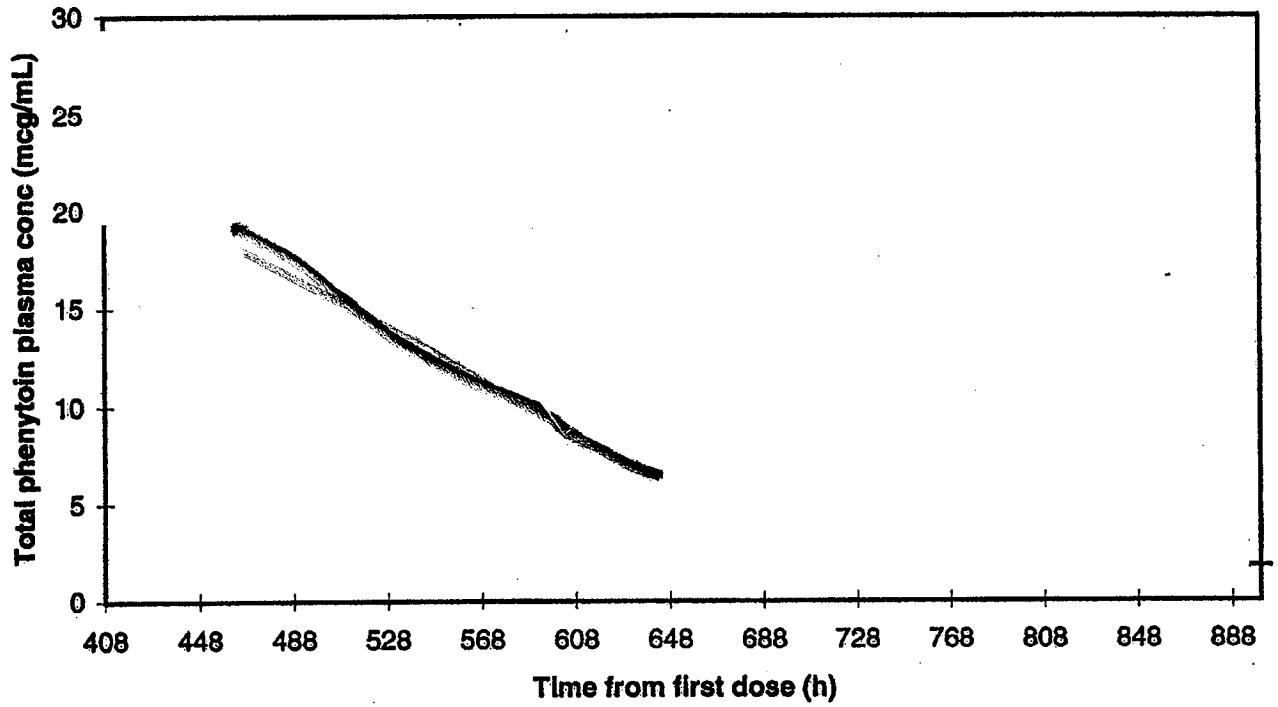
Supporting data:
Table 6. Descriptive statistics for vigabatrin concentrations (µg/mL) in plasma over time *page 14*
Appendix C.2.2.4 Listings of plasma concentration over time for vigabatrin *page 754*



b(4)

Figure 7. Total phenytoin plasma concentration over time for subject VGST1849-0009 beginning on day 10 at trough through day 12, 12 hours postdose (times are relative to the morning phenytoin dose)

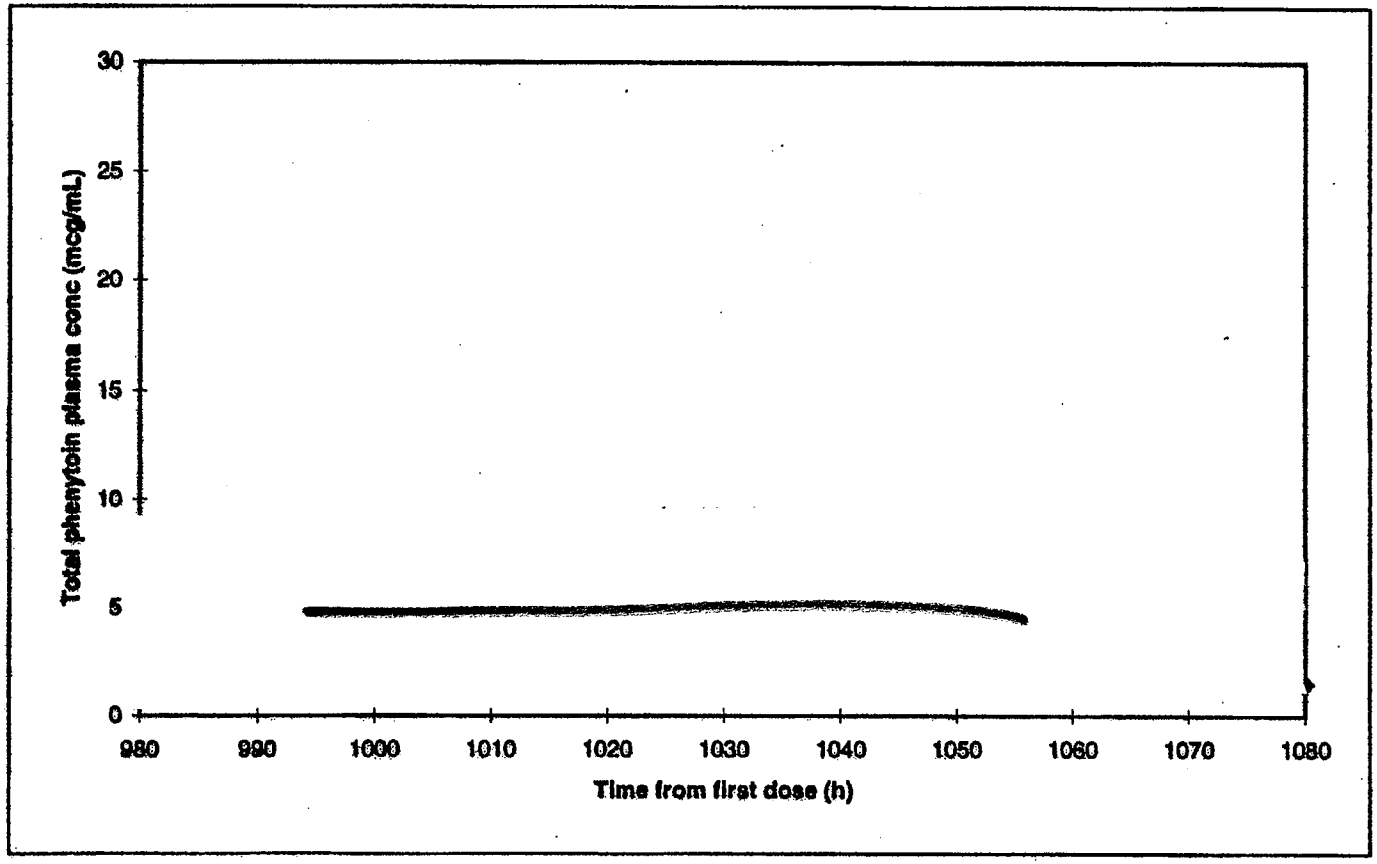
Supporting data:
Appendix C.2.2.1 Listing of plasma concentration over time for total phenytoin *page 741*



b(4)

Figure 8. Total phenytoin plasma concentration over time for subject VGST1849-0009 beginning on day16 at trough through day 37 at trough (immediately prior to the morning phenytoin dose).

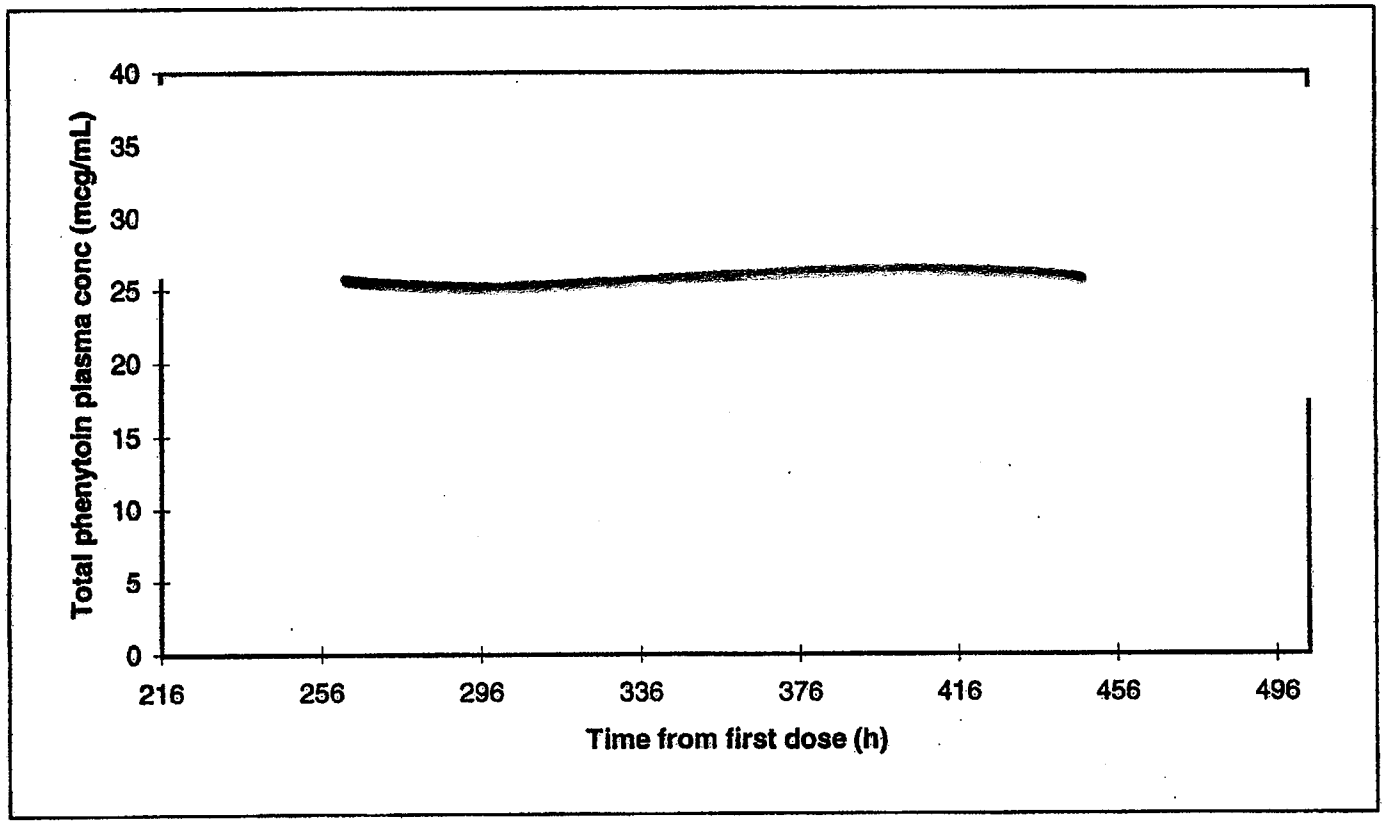
Supporting data
Appendix C.2.2.1 Listings of plasma concentration over time for total phenytoin *page 741*



b(4)

Figure 9. Total phenytoin plasma concentration over time for subject VGST1849-0009 beginning on day 42 at trough through day 46, 12 hours following the morning dose

Supporting data:
Appendix C.2.2.1 Listings of plasma concentration over time for total phenytoin *page 741*

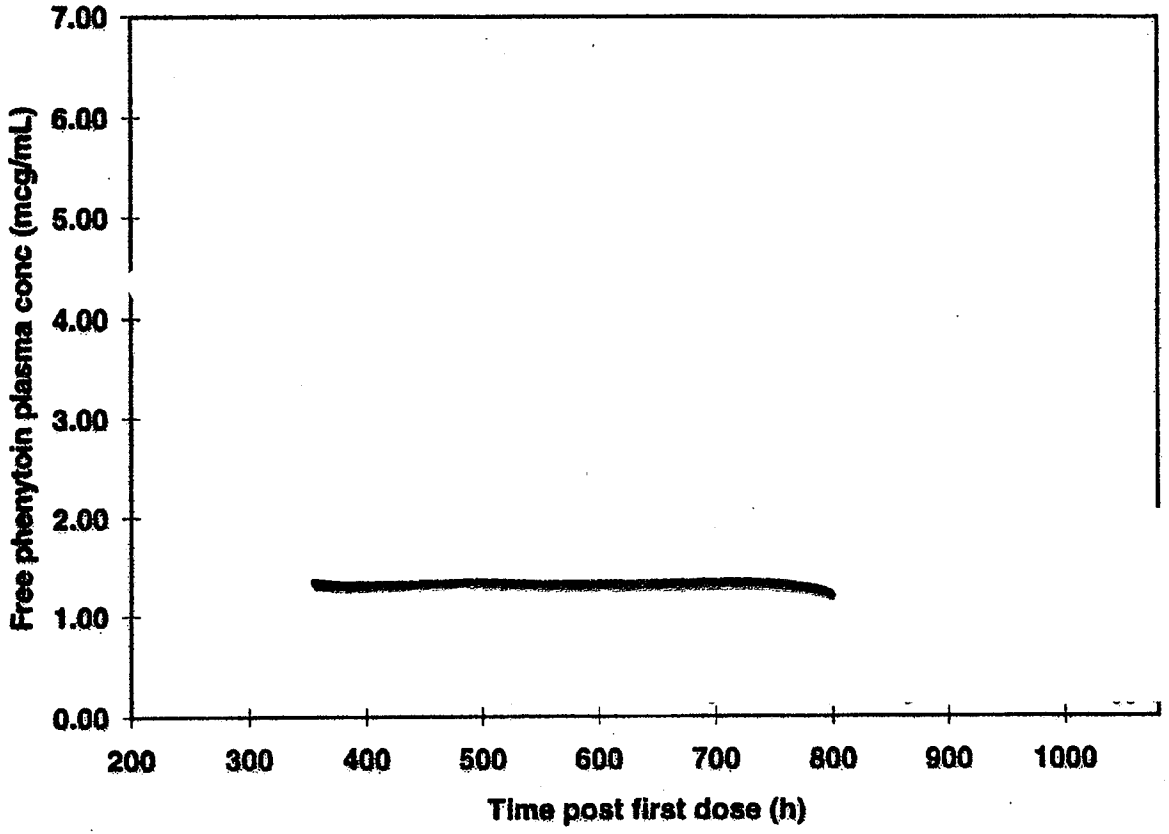


b(4)

Figure 10. Total phenytoin plasma concentration over time for subject VGST1849-0010 following administration of 150 mg phenytoin tablets every 12 hours with addition of vigabatrin 500 mg every 12 hours beginning on day 13

Supporting data:
Appendix C.2.2.1 Listings of plasma concentration over time for total phenytoin

page 741



b(4)

Figure 11. Free phenytoin plasma concentrations over time for subjects VGST1849-0009 and 0010
Supporting data:
Appendix C.2.2.3 Listings of plasma concentration over time for free (unbound) phenytoin

page 751

ATTACHMENT 2

5. INTERIM ANALYSIS

Previous data regarding the potential drug-drug interaction between phenytoin and vigabatrin suggested that the interaction may take as long as 6 weeks to come to equilibrium. There was a desire to investigate the interaction for a period shorter than 6 weeks in order to reduce the exposure of these drugs in normal healthy subjects. The study was designed so that the interaction after 3 weeks of coadministration could be compared to the interaction after 6 weeks of coadministration.

Five of the planned 15 subjects were enrolled and 4 of the 5 subjects completed the trial. An interim analysis comparing 3 weeks versus 6 weeks was conducted with data from the 4 completed subjects. The primary variables to be analyzed were $AUC(0\text{-}12\ h)_{,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for total phenytoin concentration and the secondary variables to be analyzed were $AUC(0\text{-}12\ h)_{,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for free (unbound) phenytoin concentrations.

To estimate the interaction effect, an ANOVA (terms for subject and day) was done on the natural log transformed data. From this ANOVA, least squares means for each day, estimated differences between days, and 90% confidence intervals for differences between days were calculated. These log transformed results were transformed to the original scale by exponentiation antilogs to obtain adjusted means, ratios of day means, and 90% confidence intervals for these ratios.

In order for the study to be shortened to a 3 week coadministration instead of a 6 week, the following criteria were to be satisfied.

1. The change in phenytoin $AUC(0\text{-}12\ h)_{,ss}$ between 12 days (phenytoin alone) and 3 weeks should be sufficient to characterize the pharmacokinetics of phenytoin following coadministration of phenytoin and vigabatrin.
   The probability that the upper limit for the 90% confidence interval for the ratio of mean AUC for day 44 versus day 12 was less than 85% (corresponding to a decrease of 15% based on data from previous studies) was calculated. The ratio of mean phenytoin AUC for day 44 versus day 12 should be less than or equal to 85%.

2. Phenytoin AUC after 3 weeks of coadministration should be similar to after 6 weeks of coadministration.
   Using the intrasubject CV for $AUC(0\text{-}12\ h)_{,ss}$ calculated from the ANOVA, the probability that the 90% confidence interval for the ratio of means for day 65 versus day 44 is entirely within (70, 143)% was calculated, assuming that the true ratio was between 95% and 105%. This probability was to be at least 80%.

The following are the descriptive statistics and estimates of the ratios and 90% confidence intervals for the $AUC(0\text{-}12\ h)_{,ss}$ of total phenytoin.

Day	Mean	SD	Adjusted Mean	Pairwise comparisons		
				Pair	Ratio (%)	90% CI
12	103.86	30.36	100.99	day 44 / day 12	66.4	(59.1, 74.7)
44	68.19	14.64	67.07	day 65 / day 44	97.7	(86.9, 109.8)
65	68.70	25.65	65.50	-	-	-

The results of $C_{max,ss}$ and $C_{min,ss}$ for total phenytoin were very similar to that shown for $AUC(0\text{-}12\ h)_{,ss}$. The secondary analyses of free phenytoin were also consistent with these results. The ratio of day 44 to day 12 was less than 85% which met the specifications for first criteria. The 90% confidence interval for the ratio of means of day 65 to day 44 was well within (70, 143)% demonstrating the similarity of results between 6 weeks and 3 weeks and meeting the specifications for the second criteria.

Consequently, a decision was made to amend the study to end after 3 weeks of coadministration. The protocol amendment of 19 Dec 96 addressed this change. The analysis plan and summary of data and statistics can be found in *Appendix A.6 Interim analysis, page 313.*

ATTACHMENT 3

MAR - 3 1995

Vigabatrin (SABRIL®)
500 mg Tablet

Marion Merrell Dow Inc.,
Kansas City, MO
Submission Dates:
May 2, 1994
June 14, 1994
January 6, 1995
January 10, 1995
January 16, 1995
February 23, 1995

Reviewer: Vijay K. Tammara, Ph.D.

Type of Submission: NDA 20-427 (NME)

Review of an NDA

SYNOPSIS

Vigabatrin is a selective and irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter γ-aminobutyric acid (GABA). Vigabatrin is indicated as add-on therapy for the treatment of complex partial seizures. The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS. The starting dose is 1g daily (one 500 mg tablet bid), which may be increased or decreased in 500 mg increments at weekly intervals, depending on clinical response and tolerability. The recommended maintenance dose is 3 g daily (three 500 mg tablets bid); dose can be increased to a maximum of 6 g in patients. Vigabatrin is a racemate consisting of two enantiomers. The S (+) enantiomer is active, while R (-) enantiomer is inactive. The focus of this NDA is racemate vigabatrin.

The sponsor had conducted clinical/pharmacokinetic studies using the US uncoated tablet. The eventual to-be-marketed dosage form will be the US film coated tablet. In this regard, the sponsor has performed a single dose bioequivalence study involving these two formulations. It was observed that the US film-coated and US uncoated tablets were bioequivalent based on AUC, Cmax, and Tmax.

Vigabatrin is rapidly and well absorbed reaching peak plasma concentrations in one hour (CV: 34%). The relative oral bioavailability of vigabatrin (Sabril®) 500 mg film-coated tablets is 101% (CV: 17%). Vigabatrin is widely distributed throughout the body as the steady state volume of distribution is 1.1 L/Kg (CV: 20%). Vigabatrin does not bind to plasma proteins. CSF

vigabatrin concentrations represented approximately 10% of the corresponding blood concentrations.

Following a single 1.5 g oral dose of ^{14}C-vigabatrin to 6 healthy male volunteers, an average of 95% (CV: 20%) of total radioactivity was recovered in the urine over 72 hours. The parent drug represented 82% (CV: 28%) of the dose in urine indicating that vigabatrin is essentially excreted unchanged in humans. The metabolites (vigabatrin-lactam and another unidentified metabolite) accounted for less than 5% of total dose in urine. Neither of these could be measured in plasma. Thus, the focus of this NDA is unchanged vigabatrin.

The elimination half-lives of vigabatrin and total radioactivity were 7.5 ± 2.3 hours and 9.5 ± 2.8 hours, respectively.

The degree of accumulation is minimal (1.2) and is independent of dose as seen in a multiple dose study involving 0.5 g bid and 2 g bid administrations. Vigabatrin displayed linear pharmacokinetics over the single dose range of 0.5 - 4 g. Further, dose proportionality is also seen in the dose range of 0.5 to 2.0 g bid. The intra- and inter-subject variability for vigabatrin AUC and Cmax was < 14% and < 22%, respectively. Population analysis indicated that vigabatrin did not deviate from linearity at 4 - 6 g daily dose. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentration of vigabatrin at 1.5 to 4.5 g doses.

Food decreases mean Cmax by 33% and increases mean Tmax two-fold; the extent of vigabatrin absorption was not affected.

Both the R (-) and S (+) enantiomer displayed linear pharmacokinetics over the dose range of 0.5 - 2.0 g bid. Further, it was observed that the enantiomers do not interconvert.

In epilepsy patients, vigabatrin Tmax occurred 15 minutes earlier and Cmin decreased by 28% in comparison to healthy subjects -- (mean Cmins 4.4 vs 6.1 μg/mL; CVs for both population about 25%); this was a cross study comparison. No difference was observed in the mean pharmacokinetic parameters of AUC, Cmax, and Cl.

A cross study comparison in subjects accompanied by population analysis of patient data indicated that the elderly showed a 25% decrease in clearance compared to the young; 0.8 mL/hr/Kg vs 1.1 mL/hr/Kg.

No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Across study comparison of vigabatrin pharmacokinetics between Caucasians and Japanese subjects showed that the renal clearance of Caucasians (5.2 L/hr) is about 25% higher than the Japanese (4 .0 L/hr).

Pharmacokinetics of vigabatrin following single dose of 0.75 g oral solution was evaluated in 24 subjects with varying degrees of renal function. The reviewer reclassified renal impairment into four groups, instead of three as originally provided by the sponsor; these groups are as follows:
normal (creatinine clearance CL_{cr} > 70 mL/min), mild (CL_{cr} from >50-70 mL/min), moderate (CL_{cr} from >30-50 mL/min), and severe (CL_{cr} from >10-30 mL/min).

Mean AUC∞ increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in mildly renally impaired group in comparison to normal group.
Mean AUC∞ increased by two-fold and the terminal half-life increased by two-fold in moderately renally impaired group in comparison to normal group. (Renal clearance is 3-fold less in this population).
Mean AUC∞ increased by 4.5-fold and the terminal half-life increased by 3.5-fold in severely renally impaired group in comparison to normal group. (Renal clearance is 8-fold less in this population).

Accumulation of vigabatrin can occur in both the moderate and the severe group and thus dosage adjustment is recommended. Patients with moderate and severe renal impairment should be started with a lower dose of vigabatrin and monitored for any side effects.

Total phenytoin concentrations decreased significantly (14-40%) after 4 weeks of 3 g of vigabatrin treatment. These decreased phenytoin levels returned to baseline levels in week 7. While the mean free fraction of phenytoin, with and without vigabatrin were comparable (0.15 ± .03 vs 0.16 ± .05; ↓6%), a check of individual patient data revealed that free fraction decreased by 3 --29% in 5 patients and increased by 10 -- 39% in three patients. Further, patients who had carbamazepine (CBZ) with phenytoin (n=7) showed consistent CBZ levels at baseline and the nine weeks of measurements. However, for the two patients on sodium valproate and phenytoin treatments inconsistent valproate levels were seen.

Clonazepam (0.5 mg) co-administration has no influence on the pharmacokinetics of vigabatrin (1.5 g bid, n=12). In turn, vigabatrin seems to increase the mean Cmax of clonazepam by 30% and decrease the mean Tmax by 45%.

Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g bid) indicated that neither drug influences the pharmacokinetics of the other (n=12).

Population pharmacokinetic analysis of vigabatrin by NONMEM indicated that oral clearance of vigabatrin increased with a patient's body weight and decreased with their age. Further, it was also observed that potential covariates such as race, gender, study site, and concomitant epilepsy drugs (e.g., phenytoin, carbamazepine, valproic acid, primidone, phenobarbital, and clorazepate) had no influence on the population pharmacokinetic parameters of vigabatrin.

A single dose of Vigabatrin (50 mg/kg) significantly increased total GABA levels till 120 hours post-dosing.

Relative to a 3 mg dose of lorazepam serving as a control and showing significant deterioration in cognitive function and attention tests, the three different dose levels of 1, 2, and 3 g of vigabatrin showed minimal changes.

The sponsor provided *in vitro* dissolution profiles of US film-coated vigabatrin tablets (bio-batch; the to-be-marketed dosage form) in water, 0.1 N HCl, and simulated intestinal fluid w/o enzymes (SIF). Based on the results provided the following dissolution methodology and specification is recommended for Vigabatrin 500 mg US film-coated tablets:

Medium:	900 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than [redacted] in 30 minutes

b(4)

RECOMMENDATION:

This submission (NDA 20-427) has been reviewed by the Division of Biopharmaceutics and has been found to be acceptable for meeting the Division of Biopharmaceutics' requirements. **Comments 1-3** are for the medical officer. The sponsor is requested to pursue **Comments 4 and 5** and adopt dissolution methodology and specification as outlined in **Comment 6.** Please forward **Comments 4 - 6** to the sponsor.

Table of Contents

VI. SPECIAL POPULATION STUDIES

Age

Pharmacokinetics of vigabatrin in healthy elderly subjects following a single 1.0 g oral dose (71754-1-C-023).

Gender

A definitive study evaluating the pharmacokinetics of vigabatrin in patients with epilepsy (71754-1-C-018).

Double-blind, randomized, placebo-controlled, parallel group dose response study of vigabatrin in patients with uncontrolled complex partial seizures: A population pharmacokinetic analysis (K-92-0350-CDS).

Race

A definitive study evaluating the dose proportionality of vigabatrin following single oral doses of 0.5, 1.0, 2.0, and 4.0 g (Caucasians; 71754-1-C-014).

Vigabatrin dose proportionality and pharmacokinetics following single doses of 1.0, 2.0, and 4.0 g in Japanese healthy subjects (JGVG-CL-101A).

Renal Insufficiency

A definitive study evaluating the pharmacokinetics of vigabatrin following single oral doses of 0.75 g in patients with varying degrees of renal function (71754-1-C-016).

VII. DRUG INTERACTION STUDIES

Verification and investigation of drug interaction between vigabatrin and phenytoin (S-87-0018-C).

A study to evaluate the effects of chronic dosing of vigabatrin (1500 mg bid), alone and in combination with an acute oral dose of clonazepam (0.5 mg) in healthy human volunteers (W-91-0056-C).

A double-blind 4 period crossover study to evaluate the effects of vigabatrin and ethanol, alone and in combination in human volunteers (W-91-0057-C).

VIII. POPULATION PHARMACOKINETIC ANALYSIS

Double-blind, randomized, placebo-controlled, parallel group dose response study of vigabatrin in patients with uncontrolled complex partial seizures: A population pharmacokinetic analysis (K-92-0350-CDS).

IX. PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS

Determination of Encephalotropic, Psychotropic, and Pharmacokinetic Properties of Gamma-Vinyl GABA - A Transaminase Inhibitor - by Pharmaco-EEG and Psychometry (S-84-0039-C).

X. DOSE LEVELS OF VIGABATRIN IN CSF AND CSF BIOCHEMISTRY

Suboccipital Cerebrospinal Fluid Concentrations of Vigabatrin in Patients with Epilepsy (S-84-0044-C).

The Effects of a Single Dose of Vigabatrin on the cerebrospinal fluid (CSF) Concentrations of Total and Free GABA, Homocarnosine (HC), 5-Hydroxyindole acetic acid (5-HIAA), and Homovanillic acid (HVA) in Epileptic Patients with Serial Lumbar Punctures (S-88-0014-C).

XI. PROTEIN BINDING STUDIES

To determine the binding of vigabatrin to reconstituted serum (S-81-0003-D).

APPENDIX II- Analytical Methodology

APPENDIX III- Drug Formulation

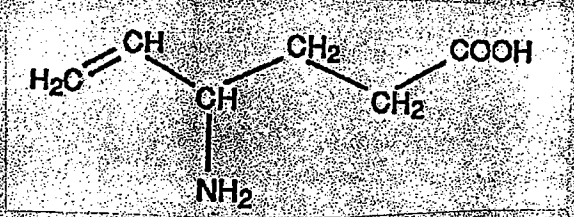
APPENDIX IV- In Vitro Dissolution

INTRODUCTION:

Vigabatrin (SABRIL®) is a selective and irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter γ-aminobutyric acid (GABA). Vigabatrin undergoes minimal metabolism and thus the focus of the NDA is unchanged vigabatrin.

Vigabatrin is an oral antiepilepsy drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The S (+) enantiomer is active, while R (-) enantiomer is inactive. The molecular formula is

$C_6H_{11}NO_2$ and the molecular weight is 129.16. It has the following chemical structure:



Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log P = -1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3 degree range within the temperature interval of 171 - 176°C. The dissociation constants (pK_a) of vigabatrin are 4.02 and 9.74 at room temperature (25°C).

INDICATIONS AND USAGE

The sponsor is proposing SABRIL as add-on therapy for the treatment of complex partial seizures with or without secondary generalization in adults.

DOSAGE AND ADMINISTRATION

For adults over 18 years of age. SABRIL is intended for oral administration twice daily. The starting dose is 1 g daily (one 500 mg tablet bid). The daily dose may be increased or decreased in 500 mg increments at weekly (or longer) intervals, depending on clinical response and tolerability. The recommended maintenance dose is 3 g daily (three 500 mg tablets bid); slight increases in efficacy may be obtained at doses up to 6 g in some patients. Adverse events increased with doses of 6 g daily in clinical trials.

MANUFACTURER:

Manufactured by Marion Merrell Dow, Inc., Kansas City, Missouri, USA.

SUMMARY OF HUMAN BIOAVAILABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS

I. BIOAVAILABILITY:

A. Relative Bioavailability:

The mean (%CV) relative bioavailability of vigabatrin was about 101% (17%) for vigabatrin 500 mg film coated tablets in comparison to an oral solution.

II. PHARMACOKINETICS:

A. Absorption:

Following multiple oral doses of 1.5 g bid in epileptic patients, mean (%CV) Cmax was 61 μg/mL (21%) with a Tmax of about 1.0 hour (34%).

B. Distribution:

Mean (%CV) steady state volume of distribution is 1.1 L/Kg (20%).

C. Metabolism (Study # 71754-1-C-027):

Vigabatrin was essentially excreted unchanged in humans as demonstrated by a radiolabelled study. Following a single 1.5 g dose (15 mL of 100 mg/mL oral solution containing 50μCi) of ^{14}C-vigabatrin to 6 healthy male volunteers, it was observed that plasma radioactivity reached mean maximal level of 49 (13%) μg Eq./mL at 0.7 hours, indicating rapid absorption. The percent of radioactivity recovered in the urine after 72 hours was found to be 95% (20%) of the administered dose. Further, it was observed that in urine 82% (28%) of the administered dose was excreted as unchanged vigabatrin. The metabolites (vigabatrin-lactam and another unidentified metabolite) accounted for less than 5% of the total dose in urine. Neither of these could be measured in plasma.

D. Elimination:

The mean apparent half-life of vigabatrin following administration of 500 mg tablet was found to be 7.5 hours (CV 31%).

III. DOSE PROPORTIONALITY:

Dose proportionality of vigabatrin was assessed from several studies by this reviewer. In a single dose study involving Caucasians, dose-proportionality of

vigabatrin at four dose levels (0.5, 1, 2, and 4 g) was evaluated in 23 normal healthy male volunteers (71754-1-C-014). AUC and Cmax of vigabatrin increased proportionally with dose, while half-lives stayed constant at about 7.0 hours across doses. Thus, it can be concluded that vigabatrin displays linear kinetics in the 0.5 - 4 g dose range.

In a multiple dose study involving Caucasians dose-proportionality was assessed at 0.5 and 2 g doses administered every 12 hours for 5 days to 24 normal healthy male subjects (71754-1-C-015). Steady state is attained within two days. Accumulation of the drug appears to be modest at multiple dosing (i.e., accumulation: 1.2; theoretical R = 1.5). Based on normalized AUC_{0-12}, Cmax, and Cmin values, vigabatrin displays linear kinetics over the dose range of 0.5 - 2.0 g bid. Further, both the R (-) and S (+) enantiomer displayed linear pharmacokinetics over the dose range of 0.5 - 2.0 g bid. It was observed that the enantiomers do not interconvert.

In another study, dose proportionality at three single dose levels of 1, 2, and 4 g was evaluated in 7 Japanese healthy male subjects (JGVG-CL-101A). The mean AUC and Cmax values for 1, 2, and 4 g doses were found to be proportional. The mean half-life decreased from 7.6 hours at 1 g dose to 5.5 hours at the 4 g dose (a 30% decrease). This decrease in half-life was accompanied by a 30% decrease in the volume of distribution such that the overall clearance of the drug remained the same.

Population analysis indicated that vigabatrin did not deviate from linearity at 4 - 6 g daily dose.

The two dose proportionality studies above (Caucasian and Japanese) allow for an across race comparison which is presented under the section - Effect of Race.

IV. BIOEQUIVALENCE STUDY

The US film-coated vigabatrin tablet (the to-be-marketed formulation) was tested for equivalency with US uncoated vigabatrin tablet (which was used in clinical and pharmacokinetic studies) in 12 healthy male subjects (71754-1-C-029). 90% Confidence interval analysis (two one-sided tests procedure) using log transformed data for vigabatrin $AUC_{0-\infty}$ and Cmax indicated that the US film-coated tablets are bioequivalent to the US uncoated tablets;
AUC 99 -105%; Cmax 89 -104%. Mean Tmax was comparable (0.8 hrs). Variability in the pharmacokinetic parameters was < 20%.

V. MULTIPLE DOSE STUDY

A cross study comparison of vigabatrin pharmacokinetics between patients (n = 11; 6M/5F; 71754-1-C-018) who received 1.5 g bid for 4 days and healthy subjects who received 2 g bid for 5 days was performed (71754-1-C-015). This involved a 25% normalization of the data obtained in subjects. The demographics of the two populations are comparable. No difference was observed in the mean pharmacokinetic parameters of AUC, Cmax, and Cl; Tmax occurred 15 minutes earlier and Cmin was 28% lower in epilepsy patients in comparison to healthy subjects (mean Cmins 4.4 vs 6.1 μg/mL; CVs for both population about 25%). There was no difference in the excretion of vigabatrin in these two populations as indicated by similar CLtotal, CLr, and percent of vigabatrin recovered in the urine.

VI. FOOD EFFECT STUDY

The influence of food on the bioavailability of vigabatrin 500 mg US uncoated tablets was studied in 24 healthy male volunteers in a single dose, crossover study (71754-1-C-017). Each treatment was separated by a one week washout period. Subjects received 2 x 500 mg tablets after an overnight fast or 2 x 500 mg tablets along with a standardized calorie-rich breakfast (2 slices of toasted white bread with butter, 2 eggs fried in butter, 2 slices of bacon, 2 ounces of hash-brown potatoes, 8 ounces of whole milk). It was observed that in the presence of a calorie-rich breakfast, mean C_{max} of vigabatrin decreased 33% and mean t_{max} increased two-fold (fasted: 1 hr; fed: 2 hrs). Food increased the variability of these parameters. There was no change in AUC. Thus, oral administration of vigabatrin during a meal resulted in a slower rate of absorption compared to its administration in a fasted state.

In the bioequivalence study (protocol # 71754-1-C-029), it was seen that US film coated tablet (the to-be-marketed formulation) is bioequivalent to US uncoated tablet. Even though a direct food effect study on film coated tablets was not performed, the conclusions drawn from this food study (involving uncoated tablets), would provide for a reasonable representation of the effect of food on film coated tablets.

The effect of food on vigabatrin tablets should be noted in the labelling of this drug.

VII. SPECIAL POPULATION STUDIES

Effect of Age:

Pharmacokinetics of vigabatrin in 12 healthy elderly male subjects (mean age:

75.3 ± 6.8 years; mean wt: 77.8 ± 10.6 Kg; 71754-1-C-023) and in 24 healthy young subjects (mean age: 27.3 ± 8.2 years; mean wt: 71.6 ± 10.2 Kg; 71754-1-C-014) was evaluated in a cross-study single dose (1 g) comparison. Renal and oral clearance of vigabatrin were 33% and 20% less in elderly subjects in comparison to young subjects.

Population analysis of vigabatrin pharmacokinetics in the patient population indicated that oral clearance of the drug increased with a patient's body weight and decreased with their age. The relationship of body weight and age on clearance based on NONMEM analysis can be defined as follows:

$$Cl = 4.91 + 0.015 * Wt - 0.0286 * Age$$

From NONMEM analysis, the base model for clearance showed an objective function value (OFV) of 1892. Then, the sponsor tested one covariate at a time and obtained OFVs; these included weight, age, concomitant medication. Both weight and age separately decreased OFV by about 30 units (viz., to 1862). Simultaneous fitting of weight and age as indicated in the equation above, decreased OFV to 1826 and the resultant clearance values are: elderly: 0.8 mL/hr/Kg; young 1.1 mL/hr/Kg; a 25% decrease in clearance in the elderly.

Caution should be exercised in elderly patients due to their decreased clearance of vigabatrin (See Labelling).

Effect of Gender:

No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients (6M/5F; 71754-1-C-018). Further, population analysis (K-92-0350-CDS) also indicated that there is no gender difference in the pharmacokinetics of vigabatrin.

Effect of Race:

The sponsor did not investigate race differences in the pharmacokinetics of vigabatrin. However, in a cross-study comparison of the pharmacokinetics of vigabatrin in 23 Caucasians (71754-1-C-014) and in 7 Japanese (JGVG-CL-101A) subjects who were administered 1, 2, and 4 g doses of vigabatrin indicated that the AUC, Cmax, and half-life are comparable. The mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4 .0 L/hr). Inter-subject variability in Caucasians was observed to be ≈ 20%; in Japanese it was ≈ 30%.

Effect of Renal Insufficiency:

Pharmacokinetics of vigabatrin following single dose of 0.75 g oral solution was evaluated in 24 subjects with varying degrees of renal function (71754-1-C-016). The reviewer reclassified renal impairment into four groups, instead of three as originally provided by the sponsor; these groups are as follows: normal (creatinine clearance CL_{cr} > 70 mL/min), mild (CL_{cr} from >50-70 mL/min), moderate (CL_{cr} from >30-50 mL/min), and severe (CL_{cr} from >10-30 mL/min).

Mild vs Normal: Mean AUC∞ increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in mildly renally impaired group in comparison to normal group. Inter-subject variability for these pharmacokinetic parameters was observed to be comparable between the two groups. An increase in AUC resulted in a corresponding decrease in clearance of vigabatrin. (Renal clearance was obviously less in this group (40%)).

Moderate vs Normal: Mean AUC∞ increased by two-fold and the terminal half-life increased by two-fold in moderately renally impaired group in comparison to normal group. (Renal clearance is 3-fold less in this population). Inter-subject variability for these pharmacokinetic parameters was observed to be higher in the moderate group (CV: 35% vs 15%). Accumulation of vigabatrin can occur in the moderate group and dosage adjustment is recommended. Patients with moderate renal impairment should be started with a lower dose of vigabatrin and monitored for any side effects.

Severe vs Normal: Mean AUC∞ increased by 4.5-fold and the terminal half-life increased by 3.5-fold in severely renally impaired group in comparison to normal group. (Renal clearance is 8-fold less in this population). Accumulation of vigabatrin can occur in the severe group and dosage adjustment is recommended. Patients with severe renal impairment should be started with a lower dose of vigabatrin and monitored for any side effects.

VIII. DRUG INTERACTION STUDIES

Phenytoin: The pharmacokinetic interaction between vigabatrin and phenytoin was performed as an open trial in 8 epileptic out-patients (S-87-0018-C). All patients had been on stable doses of phenytoin for at least a month prior to the beginning of the study. In addition to phenytoin, 6 of the patients were receiving carbamazepine and 3 were receiving sodium valproate. Vigabatrin was then added to the anti-epileptic regime, initially at a dose of 1 g bid for a week and increased to 1.5 g bid for 4 weeks. The dose of vigabatrin was then decreased to 1g bid for a week and then stopped. Pharmacokinetic results indicated that total phenytoin concentrations appeared to be unaltered after 4

weeks of treatment with vigabatrin. But after 5 weeks of vigabatrin treatment (4 weeks at 3 g of vigabatrin treatment), total phenytoin concentrations decreased significantly (14-40%). These decreased phenytoin levels returned to baseline levels in week 7.
The study also involved obtaining phenytoin free fraction at baseline and at the end of 4 weeks of 3 g vigabatrin treatment. While changes in mean free fraction of phenytoin with and without vigabatrin were comparable (0.15 ± 0.03 vs 0.16 ± 0.05; ↓6%), a check of individual patient data revealed that free fraction decreased by 3 --29% in 5 patients and increased by 10 -- 39% in three patients.

The effect of phenytoin on the pharmacokinetics of vigabatrin was not followed.

This study also indicates that patients who had carbamazepine (CBZ) with phenytoin (n=7) showed consistent CBZ levels at baseline and during the nine weeks of measurements. However, for the two patients on sodium valproate and phenytoin treatments fluctuating valproate levels were seen.

Clonazepam: The interaction of vigabatrin with clonazepam was investigated in 12 healthy male volunteers (W-91-0056-C). Vigabatrin (or placebo) was administered as 1.5 g bid for two days; to the ongoing treatment on day three a single dose of clonazepam (0.5 mg) was administered. Clonazepam co-administration has no influence on the pharmacokinetics of vigabatrin. In turn, vigabatrin seems to increase the mean Cmax of clonazepam by 30% and decrease the mean Tmax by 45%. AUC values for clonazepam were not computed because the sponsor mentions that several samples were below the limit of quantification.

Alcohol: The interaction of vigabatrin with alcohol was investigated in 12 healthy male volunteers (W-91-0057-C). Vigabatrin (or placebo) was administered as 1.5 g bid for two days; to the ongoing treatment on day three a single dose of ethanol (0.6 g/kg) was administered. The results indicated a slight reduction in Cmax (11%) and AUC_{0-12} (5%) of vigabatrin when coadministered with ethanol; Tmax was prolonged by 40 minutes. It was observed that vigabatrin did not alter the pharmacokinetics of ethanol. Overall, it appears that neither drug influences the pharmacokinetics of the other.

IX. POPULATION PHARMACOKINETIC ANALYSIS

Population analysis was performed on vigabatrin pharmacokinetic data obtained in a clinical efficacy study involving 174 patients with uncontrolled complex partial seizures (K-92-0350-CDS). The clinical study was a double-blind, placebo controlled, randomized, parallel group dose response study.

These patients were already receiving other antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, valproic acid, primidone, and phenobarbital. The patients were randomized to receive placebo (45), 1 g/day vigabatrin (45), 3 g/day vigabatrin (43), and 6 g/day vigabatrin (41) titrated over 6 weeks. The regimen was maintained over the following 12 weeks. Plasma samples were collected periodically during the study for the measurement of vigabatrin and other concomitant AEDs. Pharmacokinetic analysis of plasma concentrations using NONMEM indicated that potential covariates such as race, gender, study site, concomitant AEDs, and creatinine clearance had no influence on the pharmacokinetic parameters of vigabatrin. However, it was observed that oral clearance of vigabatrin increased with a patient's body weight and decreased with their age.

X. PHARMACOKINETIC - PHARMACODYNAMIC ANALYSIS

In random order at weekly intervals, 10 healthy volunteers received single oral doses of either placebo, 1 g, 2 g, 3 g of vigabatrin or 3 mg lorazepam to evaluate cognitive function and attention tests. Relative to a 3 mg dose of lorazepam serving as a control and showing significant deterioration in cognitive function and attention tests, the three different dose levels of vigabatrin showed minimal changes.

XI. DOSE LEVELS OF VIGABATRIN IN CSF AND CSF BIOCHEMISTRY

Vigabatrin was administered in a single-blind design to 6 epileptic patients (S-84-0044-C). For the first 2 weeks, 1 g/day of vigabatrin was added to pre-existing anti-convulsant therapy; this was followed by 2 weeks of treatment with 2 g/day and then by 2 weeks of placebo. Upon completion of the placebo period, patients were placed on a chronic regimen of 1.5 to 2 g/day of vigabatrin depending upon efficacy and tolerance. The daily dose of vigabatrin administered during the three year study period ranged from 1.5 g to 4.5 g. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentrations of vigabatrin with dose. It should be noted that other concomitant AEDs were also administered to this group of patients.

Eleven patients with drug-refractory partial seizures with a mean frequency of at least 4 seizures/month received a single dose of vigabatrin as an oral solution (50 mg/kg; S-88-0014-C). Further, they were receiving at least one, but not more than two other anti-epileptic drugs. CSF vigabatrin concentrations at 6 and 24 hours represented approximately 10% of the corresponding blood concentrations. This single dose of vigabatrin significantly increased total GABA levels till 120 hours post-dosing. Similarly, HC (homocarnosine) concentrations were increased significantly at 6 hours, but by 120 hours they had decreased to predrug levels and were no longer significantly different. Free

GABA and 5-HIAA (hydroxyindole acetic acid) concentrations, on the other hand, were only significantly elevated at 72 and 120 hours; HVA (homovanillic acid) concentrations were significantly different at 72, 120, and 168 hours. Thus, significant increases of long duration in CSF concentrations of total and free GABA, HC, 5-HIAA, and HVA were seen after a single dose of vigabatrin. 5-HIAA and HVA might be related to the elevation of CNS GABA.

XI. PROTEIN BINDING STUDIES (S-81-0003-D)

Equilibrium dialysis study using reconstituted human serum indicated that vigabatrin did not bind to plasma proteins.

APPENDIX II- Analytical Methodology

Vigabatrin was quantified in plasma, whole blood, urine, and feces by high performance liquid chromatography (HPLC). In plasma vigabatrin had a limit of quantitation (LOQ) of 0.5 μg/mL and in urine the LOQ was 20 μg/mL. Overall, the analytical validation was found to be satisfactory in terms of specificity, sensitivity, linearity, precision, and accuracy. An equilibrium dialysis method was used to support protein binding determinations.

APPENDIX III- Drug Formulation

Vigabatrin tablet formulation used in the clinical trials/pharmacokinetic studies, and the proposed to be marketed formulation are not identical. Uncoated vigabatrin 500 mg tablets were used in clinical trials/pharmacokinetic studies and the sponsor is proposing to market film-coated 500 mg tablets. The composition of the vigabatrin 500 mg uncoated and film coated tablets is as follows:

Ingredient	Composition (per tablet)	
	Uncoated tablet	film-coated tablet
Vigabatrin	500.00 mg	500.00 mg
Cellulose, microcrystalline	[redacted]	
Povidone		
Starch glycolate sodium	[redacted]	
Magnesium stearate		

b(4)

For Coating:

[redacted]

APPENDIX IV- In Vitro Dissolution

The sponsor provided *in vitro* dissolution profiles of film-coated vigabatrin tablets (bio-batch; the to-be-marketed dosage form) in water, 0.1 N HCl, and simulated intestinal fluid w/o enzymes (SIF). The sponsor also provided dissolution profile of uncoated tablets in water. From the data it was observed that dissolution for the film-coated tablets is rapid in all media (greater than [redacted] dissolved in 30 minutes). Based on the results provided the following dissolution methodology and specification is recommended for Vigabatrin 500 mg film-coated tablets: b(4)

Medium:	900 mL 0. 1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than [redacted] in 30 minutes

b(4)

COMMENTS TO THE MEDICAL OFFICER:

1) Population analysis of patient data indicated that the elderly cleared the drug 25% slower than the young. While this change of 25% may not need dosage adjustment in the elderly, caution should be exercised. This has been noted in the labelling of this drug [redacted] b(4)

2) Renal impairment study indicated that clearance decreases by 30% in the mild group (Clcr > 50-70 mL/min) in comparison to the normal group (Clcr > 70 mL/min); this change in the mild group does not require dosage adjustment.

Mean clearance decreased by two-fold in the moderate group (Clcr > 30-50 mL/min) and by 4.5-fold in the severe group (Clcr > 10-30 mL/min) in comparison to normal group. Both, the moderate and the severe group should be started with a lower dose, monitored for side effects, and maintained at a lower dose. [redacted] b(4)

3) The NONMEM analysis was found to be inconclusive in one study (K-92-0349-CDS) because of inexplicable outliers and results contradicting most other studies.

COMMENTS TO BE SENT TO THE FIRM:

4) The sponsor is encouraged to investigate the pharmacokinetic interactions of vigabatrin on concomitantly administered AEDs.

5) The sponsor should study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

6) The sponsor is requested to adopt the following dissolution methodology and specification for Vigabatrin 500 mg film-coated tablet:

Medium: 900 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus: USP Apparatus II (paddle) at 50 rpm
Specification: Not less than [redacted] in 30 minutes b(4)

LABELING COMMENTS:

The firm is requested to perform the following <u>revisions</u> on the submitted annotated draft labelling:

1. The bioavailability and pharmacokinetic information for **SABRIL** tablets provided in the Pharmacokinetics portion of the Clinical Pharmacology section should be <u>replaced</u> with the following:

[redacted] b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

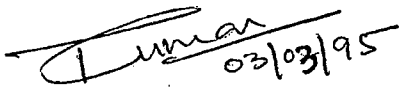
✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 19

b(4)



Vijay K. Tammara, Ph. D.
Pharmacokinetics Evaluation Branch I

Note: Dr. Raymond Miller of the Division of Biopharmaceutics reviewed and provided valuable input involving the NONMEM analysis.

First Draft prepared on January 29, 1995
Biopharm day: March 2, 1995 (Attendees: J. Collins, Ph.D.; H. Malinowski, Ph.D.; N. Fleischer, Ph. D.; M. Chen, Ph.D.; P. Hepp; R. Baweja, Ph. D.; R. Miller, Ph. D.; P. Leber, M. D.; C. McCormick, M. D.; G. Fitzgerald, Ph. D.; B. Rosslof, Ph. D)

RD/FT Initialed by R. Baweja, Ph. D. R. Baweja 3/3/95

CC: NDA 20,427 (orig.), HFD-120, HFD-426 (Tammara, Baweja, Fleischer), HFD-340 (Vish), HFD-019, Drug, Chron, Division, and Reviewer Files.

SEP 11 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Vigabatrin (SABRIL®)
500 mg Tablet
NDA 20,427

Hoechst Marion Roussel Inc.,
Kansas City, MO

Submission Dates:
May 29, 1997

FINAL
SEP 11 1997

Reviewer: **Vijay K. Tammara, Ph.D.**

Type of Submission: Response to Not Approvable Letter

In this submission, the sponsor provided responses to the Agency's "Not Approvable Letter" dated April 28, 1995 (Attachment 1).

Upon review of the responses (Attachment 2), the reviewer concurs that the sponsor has responded satisfactorily to OCPB's Comments as described below:

Comment 1: "While you have provided the results of a population based analysis of the interactions between Sabril® and other commonly administered AEDs, we suggest that you perform more formal interaction studies to examine the effects of Sabril® on plasma levels of these drugs, as well as studies to examine the effects of these other drugs on Sabril® plasma levels".

Review of Response: The sponsor is presently conducting a phenytoin-vigabatrin interaction study. OCPB will review the results of this study when submitted and the inferences will be incorporated appropriately into the labeling.

Further, the sponsor commits to evaluate any other specific drug interaction study as may be suggested by the Agency.

Comment 2: We request that you study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

Review of Response: The reviewer concurs with the sponsor's response.

Comment 3: Please adopt the following dissolution methodology and specification for Vigabatrin 500 mg film-coated tablet:

Medium:	900 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than [redacted] in 30 minutes

b(4)

Review of Response: The sponsor and OCPB came to an agreement regarding dissolution methodology and specification as outlined below, which was also incorporated in the OCPB review dated November 3, 1995.

The sponsor is requested to adopt the following dissolution methodology and specification for Vigabatrin 500 mg film-coated tablet:

Medium	:	900 mL Water at 37 ± 0.5°C
Apparatus	:	USP Apparatus II (paddle) at 50 rpm
Specification	:	Not less than [redacted] in 30 minutes

b(4)

COMMENT TO THE CLINICAL DIVISION:

1) In this submission, the sponsor has resubmitted the Original Labeling for Vigabatrin. From an OCPB standpoint, there is no new information submitted in this version of labeling. Further, OCPB's version of the original labeling has been provided in the original review of the NDA dated March 3, 1995 (Attachment 3). The clinical division is requested to incorporate these OCPB labeling changes into the labeling of this drug.

COMMENT TO BE SENT TO THE FIRM:

2) The sponsor is requested to investigate the effect of vigabatrin on the phenytoin plasma levels and vice versa in the proposed phenytoin-vigabatrin drug interaction study.

3) The sponsor is requested to adopt the following dissolution methodology and specification for Vigabatrin 500 mg film-coated tablet:

Medium	:	900 mL Water at 37 ± 0.5°C
Apparatus	:	USP Apparatus II (paddle) at 50 rpm
Specification	:	Not less than [redacted] in 30 minutes

b(4)

****

RECOMMENDATION:

This submission (NDA 20-427) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and the responses provided by the sponsor have been found to be acceptable.

Please, forward this Recommendation and Comments 2 & 3 to the sponsor.

9/11/97

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by R. Baweja, Ph. D. R. Baweja 9/11/97.

CC: NDA 20,427 (Orig.), HFD-120, HFD-860 (Tammara, Baweja, Malinowski), CDR (Barbara Murphy for Drug Files).

ATTACHMENT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-427

APR 28 1995

Marion Merrell Dow Inc.
Attention: Gregory A. Hileman, Ph.D.
US Regulatory
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Dr. Hileman:

Please refer to your pending April 29, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Sabril® (vigabatrin) 500mg tablets.

We acknowledge receipt of your amendments dated:

05-05-95	05-23-94	06-06-94	06-08-94	06-10-94	06-14-94
06-20-94	06-27-94	07-11-94	07-19-94	07-26-94	08-03-94
08-04-94	08-09-94	08-29-94	09-21-94	09-22-94	10-07-94
10-18-94	10-27-94	11-09-94	11-10-94	01-16-95	01-17-95
01-25-95	02-01-95	02-08-95	02-09-95	02-10-95	02-15-95
02-22-95	02-23-95	02-27-95	03-02-95	03-03-95	03-06-95
03-08-95	03-14-95	03-24-95	03-27-95	03-22-95	03-23-95
03-31-95	04-14-95				

Reference is also made to an Agency letter dated January 31, 1995, requesting additional Chemistry and Manufacturing Control information.

We have completed our review of your application, and have determined that it is not approvable under section 505(d) of the Act. Our review reveals that there is insufficient information to determine whether Sabril® is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(4)]. We also cannot reach a final conclusion as to the effectiveness of Sabril®.

GENERAL COMMENTS

Deficiencies in the organization, analysis and content of the new drug application have made it impossible to adequately assess the safety and effectiveness of the drug. Some of these deficiencies may be remedied by further analysis on your part, but some may reflect an irreparable lack of critical data.

The deficiencies in the application can be considered to fall into 2 general categories: 1) Inadequate collection and availability of important safety information, and 2) Inadequate analysis and reporting of information collected relative to both effectiveness and safety. Because of these

deficiencies it has been impossible for us to rely upon your reports of the studies you have performed. In the remainder of this letter, we will enumerate specific problems that we have been able to identify in these 2 categories. Because the flaws in the application are so serious, however, we cannot be certain that we have identified all the relevant problems with the application or the drug itself.

Safety concerns are most critical, particularly given the long history of a concern with findings of intramyelinic edema in multiple animal species at doses close to those used clinically. Many of our concerns arise from the unavailability of the primary Case Report Forms (CRFs) for European patients in the CRF database. Without secure knowledge of results in at least a portion of the patients exposed to Sabril® in European trials, the available safety data base that can be fully assessed is the domestic data base of somewhat over 500 patients, not, we believe, an adequate-sized exposure. The unavailability of European CRFs is perplexing to us, given that the studies from which the data in the CRFs was generated were conducted by your European affiliate. Although regulations require that you submit with the initial application only those CRFs for patients who died or discontinued treatment due to adverse events, regulations also require (21 CFR 314.50(f)(3)) that a sponsor submit additional CRFs needed to conduct a proper review as requested by the Agency.

Access to these primary records for our review is particularly critical in this case, because in our review of CRFs that have been submitted we have discovered important data that have not been reported in study reports. Because of these findings (examples of which are detailed below), we cannot be confident that your study reports accurately reflect the data as collected. Without the ability to review these primary records, we are unable to confirm your conclusions about the safety of the drug that derive from studies for which CRFs are not available. Although we also detected similar serious discrepancies between the data recorded in CRFs and reported in study reports for the 2 domestic effectiveness trials (Studies 024 and 025), which contributed to our view that your study reports were potentially unreliable, because we did have access to the CRFs, we were able to re-analyze the studies using all the relevant data.

EFFECTIVENESS

You have submitted the results of two adequate and well-controlled clinical investigations that appear (but note reservations below) to provide evidence to support your claim that Sabril® is effective as adjunctive treatment for patients with partial seizures, with and without generalization. These trials do not provide evidence that doses of Sabril® greater than 3 grams/day provide any greater therapeutic benefit than that obtained at a maximum daily dose of 3 grams.

We were not able to conclude from the evidence submitted, however, that Sabril® is effective as a treatment for complex partial seizures that become generalized. As you know, you have submitted data on the effects of Sabril® on **all** partial seizures that generalize, but have not

submitted data for each individual type of partial seizure (complex partial seizures or simple partial seizures) that can generalize. As a result, we are unable to conclude that complex partial seizures that generalize, specifically, are successfully treated by Sabril®.

Our tentative positive interpretation of the evidence adduced in these two clinical trials has been possible only because of the extraordinary efforts of our medical and statistical review staff. Because their initial audit of the documents in the NDA file bearing on the efficacy of Sabril® revealed numerous troubling, and unexplained, discrepancies between the evidence presented in the summary reports you compiled and the evidence recorded in primary data sources (individual case reports and other primary records), our staff undertook a complete and independent analysis of the evidence using primary data for one of the two trials (Study 025). It is this analysis that persuades us that Study 025 is positive; given time and resource constraints, however, we have not yet conducted an independent audit of Study 024 records. If you intend to resubmit the NDA, you will need to carry out a similar audit/re-review of study 024. We believe it important to illustrate the kind of discrepancies that we found and why we consider them so disconcerting.

Our review of individual CRFs from Study 025, for example, detected a total of 32 patients who were inappropriate recipients of concomitant anti-epileptic treatment for inadequately controlled seizures (an explicit protocol violation). Your summary report identified only 24 patients with this protocol violation; a misclassification rate of 25% for so critical a factor unacceptable and difficult to explain if the process of data tabulation, transfer, and auditing that you employed in the construction of your NDA was reliable.

Another troubling finding of our review involved your attempts to quantify the number of seizures that occurred during those episodes originally described in the CRFs as "seizure flurries", "clusters", etc. As you have acknowledged, in these cases, the assignment of a specific number of seizures to these episodes were made by company monitors, on some occasions years after the trial was completed, based on discussions with the patients, families, and/or investigators. On a number of occasions, however, the number of seizures assigned were inconsistent with previously recorded data for a given patient (e.g., the number "4" was assigned as a score for a seizure flurry 1 1/2 years after the trial was completed for a patient whose mother had been able to record up to 11 seizures/day on other occasions.). Admittedly, your summaries described the "assignment" procedure in a generic way, but specific examples of the kind of data re-expression just cited are inconsistent with the generic depiction of the process and require further specific explanation. Your study report summaries, unfortunately, had no detailed discussion of these numerical assignments made retrospectively by the company monitor.

Our review of Study 025 case reports also led to the discovery of individual records in which seizure counts for subjects were not recorded during hospitalizations. This omission has the potential to introduce significant bias, yet it was not noted in your study reports.

In sum, although we are reasonably confident that the NDA provides evidence from more than a single controlled trial to support a claim that Sabril® is an effective treatment for partial complex seizures, the review that supports this judgment also shows serious and pervasive

deficiencies in the reports submitted to the NDA. These will have to be addressed in any resubmission of the NDA; specifically, a full re-review of study 024 will be needed.

SAFETY

The information provided in the NDA fails to show that Sabril® is safe for use.

While you have ostensibly provided safety data for a cohort of greater than 3000 patients who have received Sabril®, close inspection reveals that you have not adequately recorded and/or reported important information required to establish the safety and characterize the toxic potential of Sabril®.

Deficiencies in the safety data base can be characterized as falling into one of 2 types; 1) Inadequate collection of potentially important safety information, and 2) Inadequate reporting of adverse event data collected.

1) Inadequate collection of potentially important safety information

In order for the Agency to adequately assess the safety of Sabril®, and characterize the adverse events associated with its use, we must be able to review data from a sufficiently large cohort of patients followed forward in time prospectively. This cohort must be exposed to sufficiently high doses for an appropriate duration, all adverse event data must be collected contemporaneously with the conduct of the studies, and complete, or essentially complete, case ascertainment must be assured. Specifically, the status of all patients (i.e., whether or not they discontinued treatment) must be known at the time their contribution to the safety data base ends. For example, a given patient may contribute 6 months of exposure to the data base because he or she had received six months of treatment at the time of the cut-off date for data collection. In such a case, we can know with confidence the reason for such a patient not having contributed to the data base any data beyond 6 months (despite the fact that he or she might actually have continued on treatment). On the other hand, there must also be assurance that it was not an adverse event that led to discontinuation.

Your application contains data from 3 cohorts; 1)Domestic- we consider this cohort to consist of all patients who were treated with GVG in the United States (N=537), 2)CRF- this cohort consists of all patients who received GVG outside the US, and for whom data was recorded into the NDA database either directly from CRFs or from ICSs (N=1233), 3)ARF- this cohort consists of foreign patients for whom data was entered into the NDA database from secondary sources (N=1550).

We believe that the data from the Domestic cohort is complete and that there are prospective follow-up and disposition data on essentially all 537 patients. In contrast, we consider the ARF database as unreliable because the data in it have not been prospectively recorded and cannot, therefore, be considered to provide complete follow-up and disposition data on this cohort. It is the CRF data base that is critical to providing an adequate safety data base but whose status is

in question. It may be that these data can be made complete and reliable; at present, however, we cannot conclude they are.

For example, although you were very recently (April 14, 1995) able to provide a brief tabular summary of the nominal causes for discontinuations in the CRF database, the lack of primary case records makes it impossible for us to conduct an independent audit of this report. In light of the deficiencies identified in our review of your application, this presents a serious problem. Moreover, if the case reports forms are unavailable, we are perplexed as to the primary source of information used to construct the summary tabulations provided in your April 14th submission, especially in view of your repeated earlier assertions that the information provided was not available.

We are not disputing your belief that CRFs were appropriately designed to collect information on deaths and adverse events, nor your view that they would have captured these events, if they were used as intended. This, however, is irrelevant to the matter of how reliably information recorded on CRFs was transferred to ICSs, summary reports, and tables. This can only be evaluated objectively if we have access to the CRFs.

In sum, the reports provided in the application concerning the CRF database cannot be evaluated for accuracy and reliability because we do not have access to the CRFs.

In addition, you have acknowledged that information about hospitalizations (for any reason) was not systematically collected on the European CRFs. As you know, we regard hospitalizations due to adverse events as a signal of the severity of the event. Without an accurate accounting of the number of hospitalizations, we cannot adequately characterize the severity of any adverse events that may have resulted in hospitalization that might not have been recorded.

2) **Inadequate reporting of adverse event data collected**

As noted above, a detailed review of the CRFs you have submitted reveals many examples of inadequate reporting of data collected on the CRFs.

For example, in the study report for Study 006, a study performed in the US and designed specifically to monitor patients for evidence of ocular toxicity, you describe 12 patients with abnormalities and concluded that VGB had no important ocular toxicity. Review of all 45 CRFs, however, revealed 36 patients with abnormalities that may or may not have been related to treatment. Other examples of inadequate reporting include your assertion that no significant cardiovascular adverse events occurred. This statement cannot be independently confirmed because you have submitted none of the EKG data collected.

A problem that recurs in the application is the lack of complete, detailed, comprehensive reports of specific safety issues. For example, although you have collected a considerable amount of evoked response data, you have not provided a comprehensive summary report of the findings. Similarly, you have not commented upon potentially important findings seen in some of the

autopsy examinations, nor have you submitted an analysis and report of the cases of hepatic failure, even in the face of our explicit request to do so.

A particularly troublesome omission has been the absence of a single locatable report of the serious adverse events that have occurred in association with the use of VGB. Although reports of some serious events have been included in various sections of the application, we have been unable to find a single report that describes and discusses these events in a comprehensive manner. We acknowledge that there is a section titled Serious Adverse Events in the application, but this is, in reality, a list of hospitalizations (As discussed earlier in this letter, records of hospitalizations were not systematically kept, so that this categorization cannot be relied upon to include all serious adverse events that might have occurred).

Finally, once you have reliable data on all deaths that have occurred in association with treatment with Sabril®, it will be important for you to present data on Sudden Unexplained Deaths (SUDs) in the form of SUDs/per patient-years of exposure. In this way, we will be able to compare the incidence of these events with similar estimates for recently approved anti-epilepsy drugs.

In summary, the series of deficiencies described above have made it impossible for us to independently confirm or refute your conclusions that VGB is safe for the conditions of use proposed in your draft labeling. Although it is probable that data from the Domestic database may be re-analyzed and reported adequately, it appears that repairing the deficiencies in the CRF database may be more problematic, not only because you currently do not have access to them, but also because some important information may not have been collected. In the absence of reliable data from this cohort, even if the Domestic database can be repaired, the NDA would not contain data from a sufficiently large cohort to permit the conclusion that Sabril® is safe under the conditions of use.

We encourage you to pursue approval of this application; it appears probable that Sabril® will prove to be effective therapy of partial seizures. We also recommend that you consider submitting a Treatment protocol to your IND. The Treatment protocol would provide a mechanism for making the drug available to patients who could benefit from it, while serving the critical function of allowing you to accrue the patient experience necessary to establish the safety of Sabril®. The Division of Neuropharmacological Drug Products will be happy to discuss this option with you.

In addition, we have the following comments and requests for information that should be addressed:

BIOPHARMACEUTICS

1) While you have provided the results of a population based analysis of the interactions between Sabril® and other commonly administered AEDs, we suggest that you perform more formal interaction studies to examine the effects of Sabril® on plasma levels

of these drugs, as well as studies to examine the effects of these other drugs on Sabril® plasma levels.

2) We request that you study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

3) Please adopt the following dissolution methodology and specification for vigabatrin 500 mg film-coated tablet:

Medium:	900mL 0.1 N HCl at 37 ± 0.5 C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than [redacted] in 30 minutes

b(4)

ENVIRONMENTAL ASSESSMENT

Please refer to an Agency letter dated January 31, 1995, providing for deficiencies in your environmental assessment. We requested that the exact address for the site of disposal of drug substance and drug product be included in the Freedom of Information (FOI) releasable environmental assessment document. The exact addresses for the backup locations for disposal at Dow Chemical in Plaquemine, Louisiana, and Freeport, Texas, are not given.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have any questions concerning this NDA, please contact Ms. Robin M. Pitts, Consumer Safety Officer, at (301) 594-2777.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT 2

1. Biopharmaceutics

FDA listed three issues in the biopharmaceutics section of the not-approvable letter. Responses to each of these issues were submitted to FDA by telefax on May 19, 1995 and formally in writing on June 13, 1995. HMRI believes these issues were resolved to the FDA's satisfaction in subsequent communications with the Biopharmaceutics reviewer, although formal written acceptance of our proposals was not received. The proposed resolution submitted and communications surrounding those issues are reproduced here.

1. **"While you have provided the results of a population based analysis of the interactions between Sabril® and other commonly administered AEDs, we suggest that you perform more formal interaction studies to examine the effects of Sabril® on plasma levels of these drugs, as well as studies to examine the effects of these other drugs on Sabril® plasma levels."**

[Response was submitted to FDA by telefax on May 19, 1995 and formally in writing on June 13, 1995]

The Sponsor has indeed conducted a population PK study and statistical analysis of interactions with other common AEDs. The results of that analysis suggested that phenytoin levels were consistently decreased by some unknown mechanism when vigabatrin is added to existing phenytoin levels. The Sponsor is currently conducting a phenytoin-vigabatrin interaction study in 20 patients in response to that measured outcome.

No other clinically significant interactions were consistently identified in the above analyses. When considered with other evidence presented in the NDA that Sabril® is eliminated essentially unchanged in the urine and shares no known metabolic pathways with other antiepilepsy drugs (AEDs), it is our position that we have answered all reasonable and relevant questions with this data, or will do so with the results of the phenytoin interaction study.

If the agency has reason to suspect a drug interaction with a specific AED, we would propose to evaluate that drug-drug interaction issue in a phase 4 pharmacokinetic study, and ask that this be removed as an issue of approvability.

[Telephone conversation on July 10, 1995, Dr. Vijaya Tammara]

Dr. Tammara acknowledged that the interaction issues listed in the letter were not "approvability issues" and accepted the Sponsor's proposal to conduct phase 4 testing, if necessary.

[Additional information obtained since July 1995]

The Sponsor failed to recruit sufficient patients into the phenytoin interaction study as originally designed, principally due to restrictive exclusion criteria. A new protocol was written to

overcome those problems and submitted to the IND in July 1996. Patient activity for this study occurred in August and September 1996. Results were unavailable at the time of this submission.

2. We request that you study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

[Response was submitted to FDA by telefax on May 19, 1995 and formally in writing on June 13, 1995]

The renal clearance of vigabatrin (84.2 to 93.6 mL/min) is less than the commonly reported glomerular filtration of 120 mL/min. Renal absorption in the kidney tubules is most likely the primary process governing the vigabatrin excretion rate.

Vigabatrin is a zwitterion which exists primarily as the neutral species at physiologically relevant pHs. Vigabatrin's extent of ionization, partition coefficient and solubility remain essentially constant over the nominal urine pH range of 4.5 to 8.0. It is unlikely that a fluctuation in urinary pH would change the renal reabsorption of vigabatrin. Data supporting these observations are summarized in the following table:

Table E–1. Effects of pH Change on Physical/Chemical Properties of Vigabatrin

Physical/Chemical Parameter	*Lower pH (4.1–4.5)*	*Higher pH (8.0–8.4)*
Percent present as the neutral zwitterion	>70%	≅100%
Log–partition coefficient (n–octanol/water)	–2.14	–1.96
Solubility in water (mg/mL)	495	335

Consequently, the renal clearance of vigabatrin would be expected to be insensitive to changes in urinary pH and we conclude no further study is required.

[Telephone conversation on July 10, 1995, Dr. Vijaya Tammara]

Dr. Tammara stated that, assuming the solubility and clearances are as we claim, he believes it plausible not to conduct the excretion studies. He further stated that he would discuss the matter internally prior to issuing a final decision.

[Additional information obtained since July 1995]

No additional communication has transpired either confirming or denying the Sponsor plan NOT to conduct such studies. We remain committed to our earlier conclusions that the

physico-chemical nature of the drug, in combination with measured human excretion rates, support our decision not to pursue further excretion studies.

3. **Please adopt the following dissolution methodology and specification for vigabatrin 500 mg film-coated tablet:**

Medium: 900 mL 0.1 N HCl at 37 ± 0.5 C

b(4)

Apparatus: USP Apparatus II (paddle) at 50 rpm.

Specification: Not less than [redacted] in 30 minutes

[Response was submitted to FDA by telefax on May 19, 1995 and formally in writing on June 13, 1995]

[redacted]

b(4)

[redacted]

E. Other Issues
1. Biopharmaceutics

synopsis form on June 13, 1995 is attached in *Appendix E1: Biopharmaceutics: Report Number K-95-0447-D: Comparative Bioavailability of Vigabatrin Film-Coated Tablets in Healthy Volunteers, Sg–V235–P2.*

In response to the submitted dissolution specification change, Dr. Tammara called on October 4, 1995 to clarify his earlier comments. He reiterated his general agreement with our positions, stating that the biopharm issues could not be officially reviewed until the NDA was amended to fully respond to the not approvable letter.

ATTACHMENT 3

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 18

NDA 20,427
Vigabatrin (SABRIL®)
500 mg Tablet

Marion Merrell Dow Inc.,
Kansas City, MO
Submission Dates:
January 10, 1995
June 16, 1995
September 26, 1995

NOV - 3 1995

DCTIIDM

NOV 3 1995

Reviewer: Vijay K. Tammara, Ph.D.

Type of Submission: General Correspondence

Background:

Vigabatrin is a selective and irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter γ-aminobutyric acid (GABA). Vigabatrin is indicated as add-on therapy for the treatment of complex partial seizures. The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS. The starting dose is 1g daily (one 500 mg tablet bid), which may be increased or decreased in 500 mg increments at weekly intervals, depending on clinical response and tolerability. The recommended maintenance dose is 3 g daily (three 500 mg tablets bid); dose can be increased to a maximum of 6 g in patients. Vigabatrin is a racemate consisting of two enantiomers. The S (+) enantiomer is active, while R (-) enantiomer is inactive. The focus of this NDA is racemate vigabatrin.

The sponsor has conducted clinical/pharmacokinetic studies using the US uncoated tablet. The eventual to-be-marketed dosage form will be the US film coated tablet. In this regard, the sponsor has performed a single dose bioequivalence study involving these two formulations. It was observed that the US film-coated and US uncoated tablets were bioequivalent based on 90% confidence interval analysis of log transformed AUC, Cmax, and Tmax.

In the original NDA the sponsor provided in vitro dissolution profiles of US film-coated vigabatrin tablets (bio-batch; the to-be-marketed dosage form) in water, 0.1 N HCl, and simulated intestinal fluid w/o enzymes (SIF). Based on the results provided the following dissolution methodology and specification was recommended by the Agency for Vigabatrin 500 mg US film-coated tablets (review dated April 28, 1995):

Medium:	900 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than [redacted] in 30 minutes

b(4)

In the present submission, the sponsor is requesting the Agency to adopt dissolution methodology and specification they have

proposed in the original NDA, as historically they used water in all of their quality control and stability programs. The dissolution methodology and specification proposed by the sponsor is as follows:

Medium:	900 mL water at 37 ± 0.5°C	
Apparatus:	USP Apparatus II (paddle) at 50 rpm	b(4)
Specification:	Not less than [redacted] in 30 minutes	

Upon evaluation of the dissolution data, it was observed that dissolution from the film-coated tablets seems to be [redacted] in water than that seen in acidic media and simulated intestinal fluid (Appendix 1). The dissolution of uncoated tablets in water was found to be [redacted] Further, in a comparative bioavailability study vigabatrin tablets with different in vitro dissolution rates [redacted] dissolved in 30 minutes in water) were evaluated in healthy volunteers (Appendix 2). It was observed that the mean plasma concentration-time profiles are superimposable and 90% confidence intervals for all treatments were within the 80-125% bioequivalence range. Based on these in vitro/in vivo results provided by the sponsor, the following dissolution methodology and specification is recommended for vigabatrin 500 mg film-coated tablet: b(4)

Medium:	900 mL water at 37 ± 0.5°C	
Apparatus:	USP Apparatus II (paddle) at 50 rpm	b(4)
Specification:	Not less than [redacted] in 30 minutes	

Recommendation:

The sponsor is requested to adopt the dissolution methodology and specification as outlined below:

Medium:	900 mL water at 37 ± 0.5°C	
Apparatus:	USP Apparatus II (paddle) at 50 rpm	b(4)
Specification:	Not less than [redacted] in 30 minutes	

Please convey this **Recommendation** to the sponsor.

10/31/95

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

FT Initialed by M. Hossain, Ph. D. M Hossain 11/3/95

CC: NDA 20,427 (orig.), HFD-120, HFD-860 (Tammara, Hossain, Baweja, Malinowski), Drug, Chron, Division, and Reviewer Files.

APPENDIX 1

FILM-COATED TABLETS

1

TABLE ~~IV~~

RESULTS OBTAINED FOR A MULTIPLE TIME POINT DISSOLUTION OF SABRIL® TABLETS PERFORMED IN 900 ML OF WATER

Sample Identification: Batch No. C49982C.

Tab./Cap.	Sample Wt.	Percent Labeled Amount Released				
		5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Avg.						
RSD (%)						

b(4)

References

1. MJLunn, Notebook ADB-3090, pp. 20-24.

2. TJMarchioni, Notebook ADB-3052, pp. 65-67.

QC Method 405211. Paddles at 50 rpm.

APPENDIX 1

3-1690 . v1.5

FILM-COATED TABLET

TABLE 2

RESULTS OBTAINED FOR A MULTIPLE TIME POINT DISSOLUTION OF SABRIL® TABLETS PERFORMED IN 900 ML OF 0.1N HCL

Sample Identification: Batch No. C49982C.

Tab./Cap.	Sample Wt.	Percent Labeled Amount Released				
		5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1	---					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Avg.	———	———	———	———	———	———
RSD (%)						

b(4)

References

1. MJLunn, Notebook ADB-3090, pp. 14-19.
2. TJMarchioni, Notebook ADB-3052, pp. 68-70.

QC Method 405211 modified, such that water was replaced by 900 mL of 0.1N HCl as the dissolution fluid. Paddles at 50 rpm.

APPENDIX I

FILM-COATED TABLET

3

TABLE

RESULTS OBTAINED FOR A MULTIPLE TIME POINT DISSOLUTION OF SABRIL® TABLETS PERFORMED IN 900 ML OF pH 7.5 SIMULATED INTESTINAL FLUID WITHOUT ENZYMES

Sample Identification: Batch No. C49982C.

		Percent Labeled Amount Released				
Tab./Cap.	Sample Wt.	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Avg.						
RSD (%)						

b(4)

Reference

1. MJLunn, Notebook ADB-3090, pp. 25-33.

QC Method 405211 modified, such that water was replaced by 900 mL of pH 7.5 intestinal fluid as the dissolution fluid. Due to peak splitting in basic media the solutions were acidified prior to injection. Paddles at 50 rpm.

APPENDIX J

2). **Dissolution results of film-coated and uncoated tablets: The Agency is interested in reviewing individual, as well as mean dissolution results of film-coated and uncoated tablets in water, acid, and simulated intestinal fluid dissolution media.**

Individual vigabatrin dissolution results of film-coated tablets (Lot C49982) in different dissolution media are shown in Tables IV, V, and VI from Section 3 of the NDA (attached). Lot C49982 was used in the pivotal bioequivalence study comparing to the uncoated tablets (Lot C49844).

Table 4: The individual dissolution results of uncoated tablets (Lot C49844) in water are summarized in the following table:

Tablet #	Percent Drug Dissolved				
	5 min	10 min	20 min	30 min	45 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					
CV, %					

b(4)

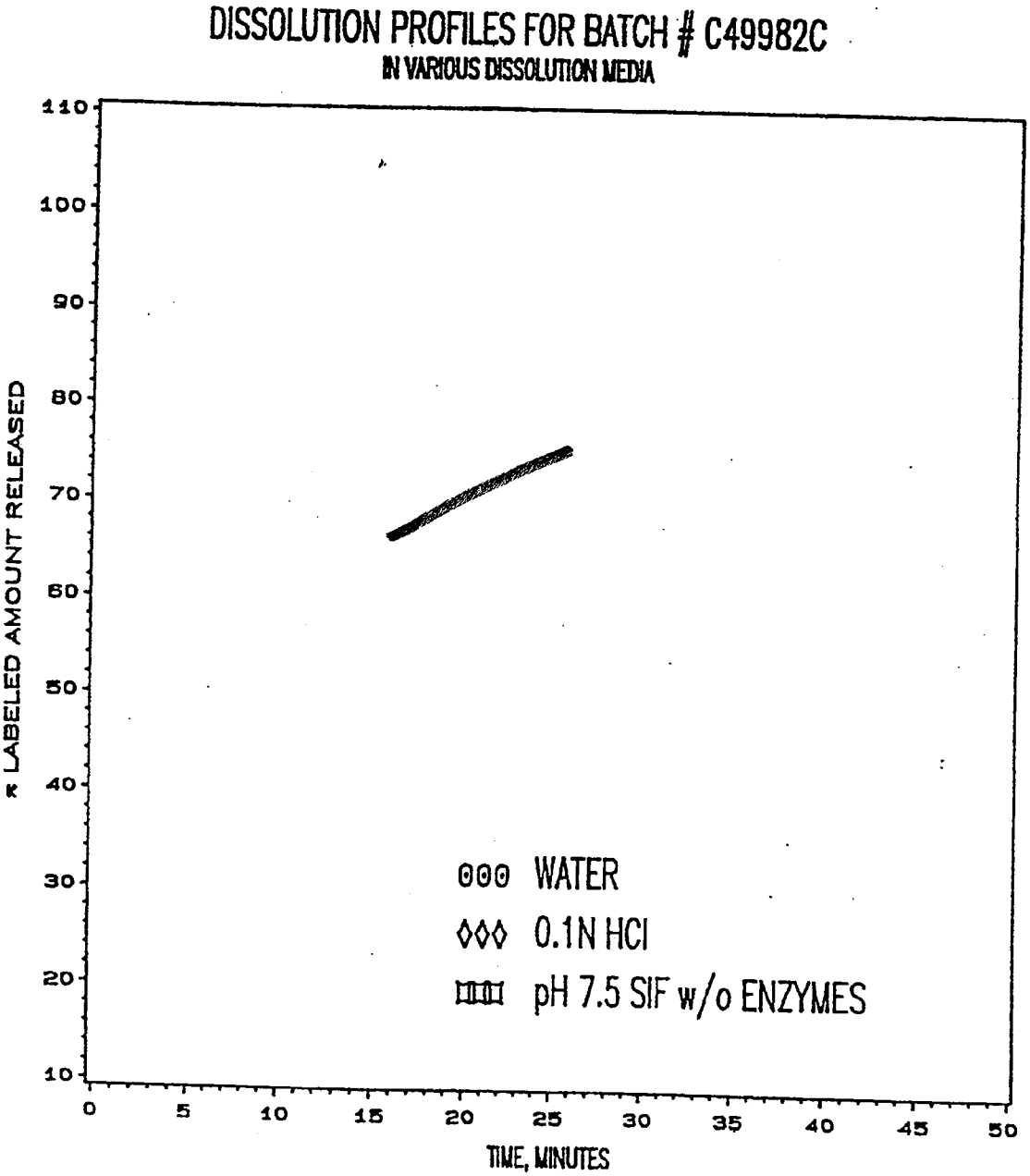
The film-coated and uncoated-tablets were shown to be bioequivalent to each other as reported in Report No. K-92-0351-DS.

APPENDIX 1

FILM-COATED TABLET

Figure 1

GRAPHICAL PRESENTATION OF DISSOLUTION PROFILE RESULTS FOR SABRIL® TABLETS IN VARIOUS DISSOLUTION MEDIA



b(4)

APPENDIX 20

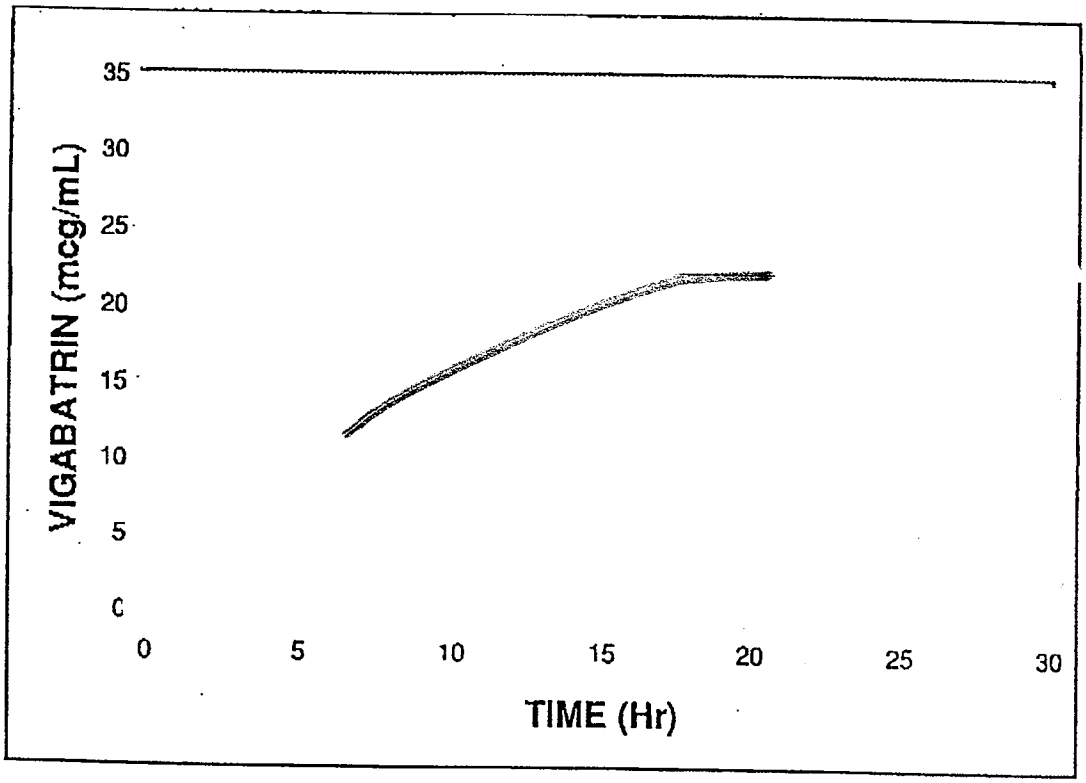
The five different film-coated Vigabatrin 500 mg tablets used in the study are described in Table 1-1.

Table 1-1. Vigabatrin Film-Coated Tablet Test Formulations

TREATMENT	LOT NO.	30 MIN DISSOLUTION, N=18 (%CV)	MANUFACTURING PROCESS
A	R51975		
B	C53733		
C	C53732		
D	R51976		
E	C53731		

b(4)

Figure 1-1



b(4)