Body System/ Preferred Term	Placebo N=119			Gabapentin N = 119	
None	62	(48.4)		44	(37.0)
Body Area Whole	20	(15.6)		39	(32.8)
Viral Infection	4	(3.1)		13	(10.9)
Fever	4	(3.1)		12	(10.1)
Headache	8	(6.3)		6	(5.0)
Weight Increase	1	(0.8)		4	(3.4)
Fatigue	2	(1.6)		4	(3.4)
Respiratory System	32	(25.0)		33	(27.7)
Pharyngitis	11	(8.6)		10	(8.4)
Upper Respiratory Infection	8	(6.3)		7	(5.9)
Rhinitis	6	(4.7)		6	(5.0)
Bronchitis	1	(0.8)		4	(3.4)
Respiratory Infection	1	(0.8)		3	(2.5)
Coughing	4	(3.1)		2	(1.7)
Nervous System	18	(14.1)		21	(17.6)
Somnolence	6	(4.7)		10	(8.4)
Convulsions	4	(3.1)		3	(2.5)
Dizziness	2	(1.6)		3	(2.5)
Hyperkinesia	1	(0.8)		3	(2.5)
Digestive System	19	(14.8)		18	(15.1)
Nausea and/or Vomiting	9	(7.0)		10	(8.4)
Diarrhea	4	(3.1)		3	(2.5)
Anorexia	3	(2.3)		2	(1.7)
Psychobiologic Function	7	(5.5)		17	(14.3)
Hostility	3	(2.3)		9	(7.6)
Emotional Lability	2	(1.6)		5	(4.2)
Special Senses	5	(3.9)		5	(4.2)
Otitis Media	4	(3.1)		1	(0.8)
Any Adverse Event	66	(51.6)		75	(63.0)

9.3.2.3 Ten Most Frequent Adverse Events In Patients In Either Treatment Group

These are shown in the next sponsor-provided table: only nausea and/or vomiting, somnolence, hostility and emotional lability can reasonably be attributed to the drug.

The higher incidence of viral infection and fever in the gabapentin-treated group in this study is not easily explained; it is noteworthy that fever was more common in the placebo-treated group in Study # 945-305/405; in the monotherapy study # 945-94, fever was marginally more common in the gabapentin-treated group and viral infection more common in the placebo-treated group; these inconsistencies might perhaps be explained by the small numbers of patients affected by these adverse events especially in the 945-86/186 and 945-305/405 studies.

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Top 10 Adverse Events Among Gabapentin-Treated Patients in Double-Blind, Placebo-Controlled Pediatric Submission Study 945-86/186 [Number (%) of Patients]				
Preferred Term	Placebo N = 128		Gabapentin N = 119	
Viral Infection	4	(3.1)	13	(10.9)
Fever	4	(3.1)	12	(10.1)
Nausea and/or Vomiting	9	(7.0)	10	(8.4)
Somnolence	6	(4.7)	10	(8.4)
Pharyngitis	11	(8.6)	10	(8.4)
Hostility	3	(2.3)	9	(7.6)
Upper Respiratory Infection	8	(6.3)	7	(5.9)
Headache	8	(6.3)	6	(5.0)
Rhinitis	6	(4.7)	6	(5.0)
Emotional Lability	2	(1.6)	5	(4.2)

9.4 Combined Adjunctive Therapy Studies

9.4.1 Overview

Adverse event data for all gabapentin-treated patients in placebo-controlled studies and their extensions are summarized in the next sponsor-provided table. As the table indicates, adverse events were more common in men than in women, and generally mild to moderate in severity.

Overview of Adverse Events (AEs) in Gabapentin-Treated Patients: Combined Adjunctive Therapy Studies 945-86/186, 945-87/187, 945/305-405, and 945-301/401						
	1 Month to <3 Years N = 115		3 to 12 Years N = 277		Combined N = 392	
Number (%) of Patients With TESS AEs						
All AEs	73	(63.5)	206	(74.4)	279	(71.2)
Associated AEs[a]	32	(27.8)	114	(41.2)	146	(37.2)
Number (%) of Patients With TESS AEs by Gender						
All AEs						
Males	45/67	(67.2)	117/140	(83.6)	162/207	(78.3)
Females	28/48	(58.3)	89/137	(65.0)	117/185	(63.2)
Associated AEs[a]						
Males	18/67	(26.9)	62/140	(44.3)	80/207	(38.6)
Females	14/48	(29.2)	52/137	(38.0)	66/185	(35.7)
Number (%) of Patients With TESS AEs by Maximum Intensity[b]						
All AEs						
Mild	44	(38.3)	76	(27.4)	120	(30.6)
Moderate	26	(22.6)	99	(35.7)	125	(31.9)
Severe	3	(2.6)	30	(10.8)	33	(8.4)
Associated AEs[a]						
Mild	24	(20.9)	39	(14.1)	63	(16.1)
Moderate	7	(6.1)	53	(19.1)	60	(15.3)
Severe	1	(0.9)	21	(7.6)	22	(5.6)
Number (%) of Deaths	0[c]		0		0	
Number (%) of Patients With Serious AEs	9	(7.8)	23	(8.3)	32	(8.2)
Number (%) of Patients Withdrawn Due to AEs						

All AEs	1	(0.9)	21	(7.6)	22	(5.6)
Associated AEs[a]	0	(0.0)	21	(7.6)	21	(5.4)

TESS = Treatment-emergent signs and symptoms.
[a] AEs that the investigator considered definitely, probably, or possibly related to study medication, and those events for which there was insufficient information to make a determination of relationship.
[b] Intensity was missing for one patient.
[c] One patient in Study 945-301/401 died after the cut-off date for the interim safety report of this ongoing study. Details of this death are in Section 6.1, Deaths.

One death occurred.

A 21-month male child (# 075501) participating in Study 945-301had intractable seizures and gastroesophageal reflux. Oral anticonvulsant medications received during the extension study were gabapentin, carbamazepine and clonazepam. On Day 64 of the study the patient underwent a Nissen fundoplication and gastrostomy on account of reflux; this was an elective procedure and the patient received his regular medications on the morning of surgery. Anesthesia consisted of nitrous oxide and propofol. Post-operatively the patient was treated with intravenous phenytoin and rectal diazepam, but oral anticonvulsant medication was not resumed. On Day 65 the patient developed a fever and worsening seizures, and was noted to be in cardiopulmonary arrest on Day 66; attempts at resuscitation failed

9.4.2 Adverse Events Occurring In ≥ 2% Of Gabapentin-Treated Patients

These were as indicated in the following table, provided by the sponsor. The most common of these were somnolence, fever, nausea and/or vomiting, pharyngitis, rhinitis, viral infection, upper respiratory infection, hostility, and otitis media (all occurring in ≥ 5 % of patients).

All Adverse Events (≥2% of Patients) by Decreasing Frequency:
ombined Adjunctive Therapy Studies 945-86/186, 945-87/187, 45-305/405, and 945-301/401
[Number (%) of Patients]

	Gabapentin	
Preferred Term	N = 392	
Somnolence	63	(16.1)
Fever	42	(10.7)
Nausea and/or Vomiting	39	(9.9)
Pharyngitis	37	(9.4)
Rhinitis	32	(8.2)
Viral Infection	28	(7.1)
Upper Respiratory Infection	28	(7.1)
Hostility	20	(5.1)
Otitis Media	20	(5.1)
Headache	19	(4.8)
Diarrhea	19	(4.8)
Convulsions	19	(4.8)
Emotional Lability	18	(4.6)
Ataxia	16	(4.1)
Rash	15	(3.8)
Fatigue	14	(3.6)
Anorexia	12	(3.1)
Hyperkinesia	12	(3.1)
Bronchitis	12	(3.1)
Gastroenteritis	10	(2.6)
Nervousness	10	(2.6)
Coughing	10	(2.6)
Respiratory Infection	10	(2.6)
Weight Increase	9	(2.3)
Abdominal Pain	9	(2.3)
Confusion	9	(2.3)
Dizziness	8	(2.0)

10. Monotherapy Studies

Protocols 945-94, a randomized controlled trial, and its open-label extension, Protocol 945-95, were studies conducted in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS). The studies are summarized in Section 2.3 and only the safety data are relevant to this application.

10.1 Demographics

As indicated in the following sponsor-provided table the demographics of the gabapentin and placebo groups were comparable at entry into the 945-94 study. Note that the age range for this study is similar to that for 945-86/186

Patient Characteristics: Pediatric Studies 945-94 and 945-95 in Children With Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS)

	Gabapentin					
	Study 945-94				Study 945-95	
Characteristic	Placebo N = 112		Gabapentin N = 114*		Gabapentin N = 191	
Sex, N (%)						
Males	65	(58.0)	70	(61.4)	121	(63.4)
Females	47	(42.0)	44	(38.6)	70	(36.6)
Age, years						
Mean (SD)	8.4	(2.3)	7.9	(2.0)	8.7	(2.2
Range	4.0, 13.0		4.0, 13.0		4.0, 14.0	
Race, N (%)						
White	85	(75.9)	83	(72.8)	145	(75.9)
Black	16	(14.3)	20	(17.5)	28	(14.7)
Asian	3	(2.7)	3	(2.6)	6	(3.1
Other	8	(7.1)	8	(7.0)	12	(6.3
Weight, kg						
Mean (SD)	35.7	(15.2)	31.5	(10.6)	36.3	(14.1)
Range	17.0, 101.8		16.7, 72.0		16.8, 105.7	
Height, cm						
Mean (SD)	133.5	(15.7)	130.7	(14.0)	134.6	(14.8)
Range	99.6, 175.3		98.6, 162.0		100.5, 170.1	

SD = Standard deviation.
* One patient in the gabapentin treatment group (Patient 9, Center 56) did not take any study medication before withdrawing from the study. Data for this patient are included in this demographics summary (N = 114), but are excluded (N = 113) from the exposure and adverse event summaries.

10.2 Exposure Data

In these 2 studies a total of 205 patients were exposed to gabapentin for 293 patient-years

Further details regarding the duration of exposure are in the following sponsor-provided table. The 945-94 study lasted 36 weeks and the 945-95 study lasted 96 weeks.

Duration of Exposure to Gabapentin: Pediatric Studies 945-94 and 945-95 in Children With BECTS [Number (%) of Patients]		
Duration of Exposure[a]	Gabapentin Studies 945-94 and 945-95 N = 205	
≥ 1 Dose	202[b]	(98.5)
≥ 1 Week	200	(97.6)
≥ 2 Weeks	199	(97.1)
≥ 4 Weeks	193	(94.1)
≥ 6 Weeks	190	(92.7)
≥ 8 Weeks	187	(91.2)
≥ 10 Weeks	186	(90.7)
≥ 12 Weeks	185	(90.2)
≥ 18 Weeks	181	(88.3)
≥ 22 Weeks	180	(87.8)
≥ 24 Weeks	177	(86.3)
≥ 26 Weeks	174	(84.9)
≥ 28 Weeks	171	(83.4)
≥ 34 Weeks	170	(82.9)
≥ 36 Weeks	167	(81.5)
≥ 38 Weeks	158	(77.1)
≥ 40 Weeks	157	(76.6)
≥ 46 Weeks	155	(75.6)
≥ 48 Weeks	151	(73.7)
≥ 50 Weeks	149	(72.7)
≥ 52 Weeks	146	(71.2)
≥ 56 Weeks	143	(69.8)
≥ 60 Weeks	139	(67.8)
≥ 64 Weeks	133	(64.9)
≥ 68 Weeks	124	(60.5)
≥ 72 Weeks	120	(58.5)
≥ 76 Weeks	114	(55.6)
≥ 80 Weeks	109	(53.2)
≥ 84 Weeks	101	(49.3)
≥ 88 Weeks	90	(43.9)
≥ 92 Weeks	85	(41.5)
≥ 96 Weeks	76	(37.1)
≥ 100 Weeks	60	(29.3)
≥ 104 Weeks	47	(22.9)
≥ 112 Weeks	28	(13.7)
≥ 120 Weeks	18	(8.8)
Total Patient-Days	106922.0	
Total Patient-Weeks	15274.6	
Total Patient-Years	292.7	

BECTS = Benign childhood epilepsy with centrotemporal spikes
[a] Includes days on which gabapentin dosing was briefly interrupted (gabapentin dose = 0 mg).
[b] Excludes 3 patients from Study 945-95: Patient 2 (Center 49) and Patient 2 (Center 66) because of missing dosing records and Patient 4 (Center 34) because of a total daily dose entry of zero.

10.3 Adverse Events

10.3.1.1 Overview

An overall summary of adverse events for both studies is presented in the following table, provided by the sponsor. In Study 945-94, adverse events were

more common in those treated with gabapentin than in those treated with placebo. Adverse events were also in general mild to moderate in severity, and more common in female children than in male children. No deaths occurred. Serious adverse events and adverse event dropouts were more common in those treated with gabapentin than in those treated with placebo in Study 945-94

Overview of Adverse Events (AEs): Studies 945-94 and 945-95

	Study 945-94				Study 945-95	
	Placebo N = 112		Gabapentin N = 113		Gabapentin N = 191	
Number (%) of Patients with TESS AEs						
All AEs	81	(72.3)	91	(80.5)	162	(84.8)
Associated AEs[a]	28	(25.0)	41	(36.3)	66	(34.6)
Number (%) of Patients with TESS AEs by Gender						
All AEs						
Males	48/65	(73.8)	55/70	(78.6)	100/121	(82.6)
Females	33/47	(70.2)	36/43	(83.7)	62/70	(88.6)
Associated AEs[a]						
Males	19/65	(29.2)	25/70	(35.7)	36/121	(29.8)
Females	9/47	(19.1)	16/43	(37.2)	30/70	(42.9)
Number (%) of Patients with TESS AEs by Maximum Intensity						
All AEs						
None	31	(27.7)	22	(19.5)	29	(15.2)
Mild	56	(50.0)	53	(46.9)	90	(47.1)
Moderate	24	(21.4)	33	(29.2)	65	(34.0)
Severe	1	(0.9)	5	(4.4)	7	(3.7)
Associated AEs[a]						
None	84	(75.0)	72	(63.7)	125	(65.4)
Mild	22	(19.6)	33	(29.2)	43	(22.5)
Moderate	6	(5.4)	7	(6.2)	22	(11.5)
Severe	0	(0.0)	1	(0.9)	1	(0.5)
Number of Deaths	0		0		0	
Number (%) of Patients With Serious AEs	1[b]	(0.9)	7	(6.2)	10	(5.2)
Number (%) of Patients Withdrawn Due to AEs						
All AEs	0	(0.0)	4	(3.5)	6	(3.1)
Associated AEs[a]	0	(0.0)	4	(3.5)	6	(3.1)

[a] AEs that the investigator considered to be definitely, probably, or possibly related to study medication, and those events for which there was insufficient information to make a determination of relationship.
[b] Non-TESS event.

Serious adverse events that occurred in Study # 945-94 are listed in the next table; the number of patients with each adverse event is listed in parentheses

Placebo	Gabapentin
Study drug overdose (1)	Suicidal ideation and hostility (1) Pneumonia (2) Fracture (1) Study drug overdose (2) Renal contusion (1)

Adverse event dropouts that occurred in Study # 945-94 are listed in the next table; the number of patients with each adverse event is listed in parentheses

Placebo	Gabapentin
None	Emotional lability (2) Hyperkinesia (1) Hyperkinesia, emotional lability and abnormal thinking (1)

10.3.2 Adverse Events Occurring In ≥ 5% Of Gabapentin-Treated Patients

These are summarized in the next sponsor-provided table. The most common of these included headache, rhinitis, viral infection, upper respiratory infection, pharyngitis, and coughing

Adverse Events (≥5% of Patients in Either Treatment Group) by Decreasing Frequency: Pediatric Studies in Children With Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS)
[Number (%) of Patients]

	Studies 945-94				Study 945-95	
	Placebo N = 112		Gabapentin N = 113		Gabapentin N = 191	
Preferred Term						
Headache	25	(22.3)	31	(27.4)	49	(25.7)
Rhinitis	20	(17.9)	23	(20.4)	34	(17.8)
Viral Infection	24	(21.4)	18	(15.9)	39	(20.4)
Upper Respiratory Infection	16	(14.3)	16	(14.2)	40	(20.9)
Pharyngitis	12	(10.7)	15	(13.3)	41	(21.5)
Coughing	7	(6.3)	12	(10.6)	16	(8.4)
Abdominal Pain	12	(10.7)	11	(9.7)	19	(9.9)
Sinusitis	7	(6.3)	10	(8.8)	16	(8.4)
Nausea and/or Vomiting	7	(6.3)	9	(8.0)	14	(7.3)
Emotional Lability	1	(0.9)	8	(7.1)	15	(7.9)
Rash	6	(5.4)	9	(8.0)	13	(6.8)
Hyperkinesia	7	(6.3)	8	(7.1)	5	(2.6)
Nervousness	0	(0.0)	8	(7.1)	5	(2.6)
Fever	5	(4.5)	7	(6.2)	19	(9.9)
Dizziness	8	(7.1)	7	(6.2)	14	(7.3)
Diarrhea	4	(3.6)	6	(5.3)	7	(3.7)
Dyspepsia	1	(0.9)	6	(5.3)	6	(3.1)
Inner Ear Infection	2	(1.8)	6	(5.3)	8	(4.2)
Fracture	1	(0.9)	4	(3.5)	10	(5.2)
Myalgia	1	(0.9)	4	(3.5)	11	(5.8)
Otitis Media	2	(1.8)	4	(3.5)	15	(7.9)
Fatigue	9	(8.0)	3	(2.7)	5	(2.6)
Thinking Abnormal	0	(0.0)	3	(2.7)	11	(5.8)
Somnolence	5	(4.5)	2	(1.8)	13	(6.8)
Weight Increase	2	(1.8)	1	(0.9)	10	(5.2)
Allergy	4	(3.6)	0	(0.0)	10	(5.2)

11. Combined Adjunctive Therapy And Monotherapy Studies

The sponsor has combined the adverse event data for gabapentin-treated patients in both groups of studies as follows

11.1 Exposure Data

Exposure data for the combined groups are in the following sponsor-provided table

Duration of Exposure to Gabapentin: Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95		
Duration of Exposure[a]	Gabapentin N = 597	
≥ 1 Dose	594[b]	(99.5)
≥ 1 Week	571	(95.6)
≥ 2 Weeks	562	(94.1)
≥ 4 Weeks	531	(88.9)
≥ 6 Weeks	480	(80.4)
≥ 8 Weeks	466	(78.1)
≥ 10 Weeks	436	(73.0)
≥ 12 Weeks	424	(71.0)
≥ 14 Weeks	402	(67.3)
≥ 16 Weeks	389	(65.2)
≥ 18 Weeks	383	(64.2)
≥ 20 Weeks	377	(63.1)
≥ 22 Weeks	364	(61.0)
≥ 24 Weeks	341	(57.1)
≥ 26 Weeks	301	(50.4)
≥ 28 Weeks	271	(45.4)
≥ 30 Weeks	261	(43.7)
≥ 32 Weeks	256	(42.9)
≥ 34 Weeks	251	(42.0)
≥ 36 Weeks	237	(39.7)
≥ 38 Weeks	197	(33.0)
≥ 40 Weeks	171	(28.6)
≥ 42 Weeks	160	(26.8)
≥ 44 Weeks	158	(26.5)
≥ 46 Weeks	158	(26.5)
≥ 48 Weeks	152	(25.5)
≥ 50 Weeks	150	(25.1)
≥ 52 Weeks	146	(24.5)
≥ 56 Weeks	143	(24.0)
≥ 60 Weeks	139	(23.3)
≥ 64 Weeks	133	(22.3)
≥ 68 Weeks	124	(20.8)
≥ 72 Weeks	120	(20.1)
≥ 76 Weeks	114	(19.1)
≥ 80 Weeks	109	(18.3)
≥ 84 Weeks	101	(16.9)
≥ 88 Weeks	90	(15.1)
≥ 92 Weeks	85	(14.2)
≥ 96 Weeks	76	(12.7)
≥ 100 Weeks	60	(10.1)
≥ 104 Weeks	47	(7.9)
≥ 112 Weeks	28	(4.7)
≥ 120 Weeks	18	(3.0)
Total Patient-Days	158793.0	
Total Patient-Weeks	22684.7	
Total Patient-Years	434.8	

[a] Includes days on which gabapentin dosing was briefly interrupted (gabapentin dose = 0 mg).
[b] Excludes 3 patients from Study 945-95: Patient 2 (Center 49) and Patient 2 (Center 66) because of missing dosing records and Patient 4 (Center 34) because of a total daily dose entry of zero.

11.2 Overview Of Adverse Events

A summary is in the following sponsor-provided table. As will be seen, overall adverse events were slightly more common in male children than in female children

Overview of Adverse Events in Gabapentin-Treated Patients: Studies 945-305/405, 945-301/401, 945-86/186, 945-87/187, 945-94, and 945-95		
	Gabapentin N = 597	
Number (%) of Patients with TESS AEs		
All AEs	466	(78.1)
Associated AEs[a]	240	(40.2)
Number of Patients with TESS AEs by Gender		
All AEs		
Males	274/333	(82.3)
Females	192/264	(72.7)
Associated AEs[a]		
Males	133/333	(39.9)
Females	107/264	(40.5)
Number (%) of Patients with TESS AEs by Maximum Intensity		
All AEs		
None		
Mild	209	(35.0)
Moderate	211	(35.3)
Severe	45	(7.5)
Associated AEs[a]		
None		
Mild	126	(21.1)
Moderate	89	(14.9)
Severe	24	(4.0)
Number of Deaths[b]	0	
Number (%) of Patients With Serious AEs	45	(7.5)
Number (%) of Patients Withdrawn Due to AEs		
All AEs	32	(5.4)
Associated AEs[a]	31	(5.2)

[a] Adverse events the investigator considered definitely, probably, or possibly related to study medication, and events for which there was insufficient information to make a determination of relationship.

[b] The ISS database contains no patient deaths; however, one patient in the ongoing gabapentin open-label studies (945-301/401) died after the cut-off date for the ISS database. Details of this death are in Section 6.1, Deaths.

11.3 Adverse Events Occurring In ≥ 2% Of Gabapentin-Treated Patients

These are summarized in the next sponsor-provided table. The most common adverse events appear related to intercurrent illnesses common in childhood rather than to gabapentin

Adverse Events (≥2% of Patients) by Decreasing Frequency: Combined Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95 [Number (%) of Patients]		
Preferred Term	Gabapentin N = 597	
Pharyngitis	88	(14.7)
Headache	82	(13.7)
Rhinitis	82	(13.7)
Somnolence	78	(13.1)
Upper Respiratory Infection	77	(12.9)
Viral Infection	77	(12.9)
Fever	68	(11.4)
Nausea and/or Vomiting	61	(10.2)
Emotional Lability	42	(7.0)
Otitis Media	39	(6.5)
Rash	36	(6.0)
Abdominal Pain	35	(5.9)
Coughing	35	(5.9)
Diarrhea	30	(5.0)
Hostility	28	(4.7)
Dizziness	26	(4.4)
Sinusitis	26	(4.4)
Hyperkinesia	25	(4.2)
Nervousness	23	(3.9)
Fatigue	22	(3.7)
Bronchitis	21	(3.5)
Weight Increase	20	(3.4)
Convulsions	19	(3.2)
Fracture	19	(3.2)
Inner Ear Infection	19	(3.2)
Insomnia	18	(3.0)
Ataxia	17	(2.8)
Thinking Abnormal	17	(2.8)
Gastroenteritis	16	(2.7)
Myalgia	16	(2.7)
Anorexia	15	(2.5)
Dyspepsia	14	(2.3)
Increased Appetite	13	(2.2)
Epistaxis	12	(2.0)
Skin Laceration	12	(2.0)
Urinary Incontinence	12	(2.0)
Any Adverse Event	466	(78.1)

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12. Approved NDA (20235) Clinical Experience

These data are for 42 patients < 12 years old included in the original "adult" NDA (# 20235) which was approved 12/30/93

12.1 Demographics

These are summarized in the following table, provided by the sponsor.

Demographics of Patients Who Received Gabapentin in Studies Summarized for the Approved NDA		
	N = 42	
Sex, N (%)		
Males	25	(60)
Females	17	(40)
Race, N (%)	N = 37[a]	
White	32	(86)
Black	4	(11)
Other	1	(3)
Age, years		
Mean	7.7	
Median	8	
Range	3 to 11	
Duration of Epilepsy, years	N = 37[a]	
Mean	2.5	
Median	< 1	
Range	<1 to 11	
Concurrent AEDs[b], N (%)		
0[c]	29	(69)
1	3	(7)
2	6	(14)
>2	4	(10)

AEDs = Antiepileptic drug.
[a] Not specified for remaining patients
[b] Based on demographic information of first study patient participated in if patient was included in more than one study
[c] Studies 945-19/-20/-49/-50 were monotherapy studies whose safety data were summarized in the Approved NDA.

12.2 Exposure Data

These are summarized below in a table provided by the sponsor.

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Summary of Pediatric Patient Exposure to Gabapentin in Studies Summarized for the Approved NDA [Number (%) of Patients]		
Total Exposure	Gabapentin N = 42	
≥1 dose	42	(100.0)
≥1 week	42	(100.0)
≥2 weeks	42	(100.0)
≥4 weeks	41	(97.6)
≥6 weeks	39	(92.9)
≥8 weeks	30	(71.4)
≥10 weeks	28	(66.7)
≥12 weeks	27	(64.3)
≥14 weeks	26	(61.9)
≥16 weeks	24	(57.1)
≥18 weeks	20	(47.6)
≥20 weeks	19	(45.2)
≥22 weeks	16	(38.1)
≥24 weeks	16	(38.1)
≥26 weeks	14	(33.3)
≥28 weeks	12	(28.6)
≥30 weeks	7	(16.7)
≥32 weeks	6	(14.3)
≥34 weeks	6	(14.3)
≥36 weeks	6	(14.3)
≥40 weeks	4	(9.5)
≥44 weeks	2	(4.8)
≥48 weeks	2	(4.8)
≥52 weeks	2	(4.8)
≥64 weeks	2	(4.8)
≥78 weeks	2	(4.8)
≥90 weeks[a]	1	(2.4)
Total Patient-Days	7090	
Total Patient-Weeks	1013	
Total Patient-Years	19.4	

[a] Patient withdrew in Week 195.

12.3 Adverse Events Occurring In ≥ 5% Of Gabapentin-Treated Patients

These are summarized in the next sponsor-provided table. The most common adverse events appear related to intercurrent illnesses common in childhood rather than to gabapentin.

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Most Frequent (≥5%) Adverse Events for Pediatric Patients in Studies Summarized for the Approved NDA [Number (%) of Patients]		
	All Gabapentin N = 42	
Preferred Term	All	
None	14	(33)
Convulsion	6	(14)
Somnolence	6	(14)
Bronchitis	3	(7)
Diarrhea	3	(7)
Nausea and/or Vomiting	3	(7)
Rash	3	(7)
Rhinitis	3	(7)
Ataxia	2	(5)
Dizziness	2	(5)
Fatigue	2	(5)
Fever	2	(5)
Hyperkinesia	2	(5)
Urinary Incontinence	2	(5)

13. Other Pediatric Clinical Experience

13.1 Outline

This section reports safety results from a prematurely-terminated study (Protocol 945-08) already summarized in tabular form in Section 2.4.

This study was carried out in patients with pharmacotherapy-resistant epilepsy (Lennox-Gastaut syndrome)

- Of the 16 patients enrolled, 14 patients received gabapentin in either the initial 12-week double-blind, placebo-controlled phase or in the open-label extension phase
- Of the 16 patients enrolled, only 6 were < 12 years old
- In the initial double-blind, placebo-controlled phase, 9 patients received gabapentin and 7 patients received placebo. 14 patients completed this phase
- 12 patients entered the open-label phase of the study, but only 2 were able to complete that phase

13.2 Exposure

Total exposure for the 6 pediatric patients was 1363 days, 26.2 patient-weeks, or 3.7 patient-years.

13.3 Adverse Events

13.3.1 Overview

An overview of the adverse event data for all 16 patients participating in this study is in the next table, which has been provided by the sponsor. As the table indicates there were no deaths or adverse event discontinuations.

	Double-Blind Phase		Open-Label Phase
	Placebo N=7	Gabapentin N=9	All Gabapentin N=12
Number Of Patients With Any Adverse Event	6	9	7
Severity			
Mild (Number Of Patients)	3	2	2
Moderate (Number Of Patients)	3	4	3
Severe (Number Of Patients)	0	3	2
Number Of Deaths	0	0	0
Number Of Patients With Serious Adverse Events	2	3	2
Number Of Patients Withdrawn Due To Adverse Events	0	0	0

13.3.2 Serious Adverse Events

These occurred in 4 patients during double-blind or open-label treatment

- Nausea, fever and an increased seizure frequency, all on gabapentin
- Urinary tract infection in a gabapentin-treated patient
- Upper respiratory infection, pneumonia and increased seizure frequency in a patient treated with gabapentin
- Recurrent aspiration pneumonia

A further patient was diagnosed to have the Wolff-Parkinson-White syndrome prior to receiving study drug; this patient did not enter the study, but in the above table is counted as a placebo patient

13.3.3 All Adverse Events

These are summarized as follows:

- In the double-blind phase of the study, adverse events that occurred in at least 1 gabapentin-treated patient and more frequently than in those treated with placebo included: fever, increased weight, drug toxicity, tachycardia, nausea, vomiting, drooling, diarrhea, constipation, convulsions, somnolence, agitation, emotional lability, pharyngitis, upper respiratory infection, lower respiratory infection, respiratory distress, rash, skin lacerations, urinary infection, otitis media, glycosuria, increased urinary protein, hyperglycemia, hypocalcemia, reduced hematocrit, reduced red blood cell count, reduced white blood cell count, reduced serum creatinine, metabolic disorder and an increased level of antiepileptic drugs (all but rash, skin laceration, pharyngitis and convulsions occurred in only 1 patient)
- In the open-label phase of the study the following adverse events occurred in at least one gabapentin-treated patient: fever, tooth fracture, convulsions, ataxia, insomnia, emotional lability, increased irritability, pharyngitis, upper respiratory infection, lower respiratory infection, aspiration pneumonia, pneumonia, head laceration, acne, otitis media, reduced platelet count and glycosuria (all except convulsions, pneumonia and a reduced platelet count occurred in only 1 patient)

14. Deaths, Serious Adverse Events and Adverse Event Dropouts

Data regarding deaths, serious adverse events and adverse event dropouts, for all the studies subsumed under this NDA, have been summarized by the sponsor in a separate section.

14.1 Deaths

Only a single death occurred in these studies. A brief narrative is provided again below:

A 21-month male child (# 075501) participating in Study 945-301had intractable seizures and gastroesophageal reflux. Oral anticonvulsant medications received during the extension study were gabapentin, carbamazepine and clonazepam. On Day 64 of the study the patient underwent a Nissen fundoplication and gastrostomy on account of reflux; this was an elective procedure and the patient received his regular medications on the morning of surgery. Anesthesia consisted of nitrous oxide and propofol. Post-operatively the patient was treated with intravenous phenytoin and rectal diazepam, but oral anticonvulsant medication was not resumed. On Day 65 the patient developed a fever and worsening seizures, and was noted to be in cardiopulmonary arrest on Day 66; attempts at resuscitation failed

14.2 Serious Adverse Events

The most common serious adverse events in the Integrated Summary of Safety appear to have been convulsions, pneumonia, drug overdose and fractures. In reviewing the already approved NDA for gabapentin, this Division had indicated a preference that convulsions should be considered evidence of a lack of efficacy rather than an adverse event.

Adverse events that occurred prior to the cut-off date for the Integrated Summary of Safety (8/13/99) are summarized in the following sponsor-provided table: they occurred in 7.9 % of patients

Summary of Serious Adverse Events That Occurred in Any Pediatric Patient Receiving Gabapentin During a Clinical Study Through August 13, 1999 [Number (%) of Patients]		
Body System/ Preferred Term	Gabapentin N = 645	
None	594	(92.1)
Body Area Whole	15	(2.3)
Drug Overdose	5	(0.8)
Viral Infection	3	(0.5)
Dehydration	2	(0.3)
Fever	3	(0.5)
Drug Toxicity	1	(0.2)
Headache	1	(0.2)
Injury, Accidental	1	(0.2)
Salmonella	1	(0.2)
Sepsis	1	(0.2)
Respiratory System	17	(2.6)
Pneumonia	6	(0.8)
Asthma	2	(0.3)
Pharyngitis	2	(0.3)
Respiratory Distress	3	(0.5)
Respiratory Infection	2	(0.3)
Upper Respiratory Infection	3	(0.5)
Abscess, Peritonsillar	1	(0.2)
Aspiration Pneumonia	1	(0.2)
Nervous System	14	(2.2)
Convulsions	7	(1.1)
Somnolence	3	(0.5)
Confusion	2	(0.3)
Stupor	2	(0.3)
Ataxia	1	(0.2)
Hemiplegia	1	(0.2)
Intracranial Hypertension	1	(0.2)
Shunt Failure	1	(0.2)
Digestive System	6	(0.9)
Appendicitis	2	(0.3)
Nausea and/or Vomiting	3	(0.5)
Abdominal Pain	1	(0.2)
Psychobiologic Function	4	(0.7)
Hostility	2	(0.3)
Emotional Lability	1	(0.2)
Hysteria	1	(0.2)
Suicidal	1	(0.2)
Musculoskeletal System	4	(0.7)
Fracture	4	(0.7)
Skin and Appendages	5	(0.8)
Animal Bite	1	(0.2)
Contusion	1	(0.2)
Insect/Bug Bites	1	(0.2)
Skin Infection	1	(0.2)
Pruritic Rash	1	(0.2)
Special Senses	2	(0.3)
Otitis Media	2	(0.3)
Cardiovascular System	2	(0.3)
Thrombosis	1	(0.2)
Tachycardia	1	(0.2)
Laboratory Deviations	1	(0.2)
Hematuria	1	(0.2)
Metabolic and Nutritional Disorders	1	(0.2)
Metabolic Disorder	1	(0.2)
Urogenital System	2	(0.3)
Urinary Incontinence	1	(0.2)
Urinary Tract Infection	1	(0.2)
Any Serious Adverse Event	51	(7.9)

Serious adverse events that were reported for Study # 945-301/401 between 8/13/99 and 11/10/99 are reported in the next sponsor-provided table

Summary of Serious Adverse Events That Occurred in Ongoing, Open-Label Gabapentin Extension Studies (945-301/401) During the Period August 13, 1999 to November 10, 1999
(Number of Patients)

Body System/ Preferred Term	Gabapentin
Body Area Whole	4
Dehydration	2
Fever	2
Sepsis	1
Respiratory System	12
Pneumonia	6
Respiratory Distress	4
Respiratory Infection	2
Respiratory Failure	1
Aspiration Pneumonia	1
Pneumothorax	1
Nervous System	2
Hemispherectomy	1
Intracranial Hypertension	1
Digestive System	4
Anorexia	1
Diarrhea	1
Gastric Reflux	1
Oral Candidiasis	1
Vomiting	1
Cardiovascular System	1
Cardiac Failure	1
Laboratory Deviations	1
Hematuria	1
Urogenital System	1
Urinary Tract Infection	1
Any Serious Adverse Event	20

14.3 Adverse Event Dropouts

These are summarized in the next table, provided by the sponsor. The most common adverse events that led to withdrawal from study were emotional lability, hostility, hyperkinesia, and convulsions, and somnolence. As already indicated above, in reviewing the already approved NDA for gabapentin, this Division had indicated a preference that convulsions should be considered evidence of a lack of efficacy rather than an adverse event.

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Withdrawals Due to Adverse Events for All Pediatric Clinical Experience [Number (%) of Patients]		
Body System/ Preferred Term	Gabapentin N = 645	
None	607	(94.1)
Nervous System	18	(2.8)
Hyperkinesia	6	(0.9)
Convulsions	6	(0.9)
Somnolence	4	(0.6)
Ataxia	2	(0.3)
Confusion	2	(0.3)
Insomnia	2	(0.3)
Amnesia	1	(0.2)
Coordination Abnormal	1	(0.2)
Speech Disorder	1	(0.2)
Stupor	1	(0.2)
Tremor	1	(0.2)
Psychobiologic Function	16	(2.5)
Emotional Lability	8	(1.2)
Hostility	6	(0.9)
Thinking Abnormal	3	(0.5)
Personality Disorder	2	(0.3)
Agitation	1	(0.2)
Anxiety	1	(0.2)
Apathy	1	(0.2)
Nervousness	1	(0.2)
Digestive System	6	(0.9)
Anorexia	2	(0.3)
Increased Appetite	2	(0.3)
Abdominal Pain	1	(0.2)
Diarrhea	1	(0.2)
Gastroenteritis	1	(0.2)
Nausea and/or Vomiting	1	(0.2)
Body Area Whole	7	(1.1)
Fatigue	2	(0.3)
Drug Toxicity	1	(0.2)
Infectious Mononucleosis	1	(0.2)
Pain	1	(0.2)
Weight Decrease	1	(0.2)
Weight Increase	1	(0.2)
Skin and Appendages	2	(0.3)
Sweating Increased	1	(0.2)
Urticaria	1	(0.2)
Urogenital System	2	(0.3)
Urinary incontinence	2	(0.3)
Cardiovascular System	1	(0.2)
Heart Block	1	(0.2)
Any Adverse Event	35	(5.4)

14.4 Narratives

I have read through all narratives for the above deaths, serious adverse events and adverse event dropouts, and supplemented them with Case Report Forms when needed.

Based on these narratives it appears that there is a fair possibility that the following serious adverse events/adverse event dropouts were caused by gabapentin (they did not always occur grouped together as below)

- Abdominal pain, diarrhea, nausea, vomiting and anorexia
- Somnolence, confusion and impaired concentration

- Behavioral disturbances including aggression, agitation, emotional lability, hostility, and restlessness
- Urinary incontinence
- Fatigue
- Ataxia and tremor
- Rash
- Weight gain
- Atypical absence and myoclonic seizures

The frequency of these adverse events was very low.

The only death which occurred was not attributable to gabapentin

15. Clinical Laboratory Data

15.1 Combined Adjunctive Therapy And Monotherapy Studies

The sponsor has provided a table listing the number of patients with very high or very low laboratory values in these studies. This table is below

Gabapentin-Treated Patients With Very Low or Very High Clinical Laboratory Values in Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95
[Number (%) of Patients][a]

Parameter	N	Very Low		Very High	
Hematology					
Hemoglobin	542	0	(0.0)	1	(0.2)
Hematocrit	542	0	(0.0)	1	(0.2)
RBC	542	0	(0.0)	1	(0.2)
Platelets	541	6	(1.1)	7	(1.3)
White Blood Cells	542	5	(0.9)	6	(1.1)
Neutrophils	538	26	(4.8)		
Blood Chemistry					
Renal Function					
BUN	544			1	(0.2)
Electrolytes					
Potassium	542			1	(0.2)
Chloride	544			1	(0.2)
Other Chemistries					
Glucose	538	2	(0.4)	1	(0.2)
Amylase	124			2	(1.6)

Note: Cells with missing information do not have sponsor-defined ranges.
[a] Percent based on N for individual parameter.

The sponsor's criteria for very high and very low laboratory values for the parameters listed in the above table are below (the table below has also been provided by the sponsor)

Parameter	Very Low		Very High	
Age Range	< 2 years	2-12 years	< 2 years	2-12 years
Hemoglobin	≤ 7.0	≤ 6.0	≥ 20	≥ 21
Hematocrit	≤ 20	≤ 24	≥ 50	≥ 54
RBC	≤ 2.1	≤ 2.2	≥ 6.0	≥ 7.6
Platelets	≤ 100	≤ 100	≥ 600	≥ 600
White Blood Cells	≤ 2.667	≤ 2.667	≥ 25	≥ 15
Neutrophils	≤ 1.0	≤ 1.0		
BUN			≥ 17.9	≥ 17.9
Potassium			≥ 7.0	≥ 7.0
Chloride			≥ 122	≥ 122
Glucose	≤ 2.2	≤ 2.2	≥ 22.2	≥ 22.2
Amylase			≥ 120	≥ 500

Units for the above parameters are in the next table

Parameter	Units
Hemoglobin	G/dL
Hematocrit	%
RBC	X 10^{12}/L
Platelets	X 10^{9}/L
White Blood Cells	X 10^{3}/μL
Neutrophils	X 10^{3}/μL
BUN	mmol/L
Potassium	mEq/L
Chloride	mEq/L
Glucose	mmol/L
Amylase	U/L

2 types of laboratory abnormalities are discussed further below

15.1.1 Neutropenia

As the above table indicates, 26 gabapentin-treated patients had neutropenia that was < 1.0 x 10^{3}/μL

A single patient (# 2 at Center 24) experienced "severe" neutropenia (defined by the sponsor as < 0.5 x 10^{3}/μL) while receiving gabapentin in Study 945-95. His neutrophil counts were as follows

Timing of Test	Neutrophil Count (X 10^{3}/μL)
First day of placebo treatment in preceding double-blind study (945-94)	1.15
First day of open-label gabapentin treatment in 945-95	1.04
Day 120 of 945-95	1.46
Day 169 of 945-95	0.41

No follow up white blood cell counts are available for this patient who apparently had normal eosinophil and basophil counts when severely neutropenic. No adverse event was recorded and further details (such as a listing of concomitant medications) are not available either.

It is noteworthy that all patients receiving gabapentin except those in the monotherapy studies were receiving one or more additional anticonvulsants.

In the randomized, controlled trials in the combined adjunctive and monotherapy group the incidence of neutropenia < 1.0 x 10^{3}/μL in the gabapentin and placebo groups was as in the following table:

Study	Placebo N/Total (%) with neutrophils < 1.0 x 10^{3}/μL	Gabapentin N/Total (%) with neutrophils < 1.0 x 10^{3}/μL
945-94	8/112 (7.4)	10/111 (9)
945-86/186	12/119 (10.1)	9/108 (8.3)
945-305/405	3/38 (10.3)	3/38 (10.3)

As the above table indicates the incidence of neutropenia in this range was similar in the gabapentin and placebo groups

15.1.2 Alkaline Phosphatase

Eight gabapentin-treated patients had elevations in alkaline phosphatase >2000 U/L. These elevations, according to the sponsor, occurred in isolation without significant elevation of other hepatic enzymes, and were considered by the investigators to be normal variants or due to growth spurts common in a pediatric population.

The incidence of elevations in alkaline phosphatase in the randomized controlled trials in the combined adjunctive therapy and monotherapy grouping is in the next table

Study	Placebo N/Total (%) with elevated alkaline phosphatase	Gabapentin N/Total (%) with elevated alkaline phosphatase
945-94	0 (0)	0 (0)
945-86/186	10/118 (8.5)	8/119 (7.5)
945-305/405	9/36 (25.0)	3/37 (8.1)

The sponsor states that all very low and high laboratory values "either resulted from pre-existing medical conditions, or were sporadic, isolated values not associated with an adverse event or other laboratory abnormalities." Since none of these laboratory values were associated with deaths, serious adverse events or adverse event dropouts, Case Report Forms and narratives for these patients were not supplied with this submission.

I have compared the incidence of all laboratory abnormalities outside the normal range in the gabapentin and placebo groups in all 3 randomized controlled trials: 945-94, 945-86/186 and 945-305/405. The incidence of laboratory abnormalities was low, there were no items of concern, and there were no major differences between the 2 treatment groups.

15.2 Pediatric Experience In Approved NDA

Clinical laboratory values for the 42 pediatric patients from the approved NDA population showed no clinically important abnormality.

The same observation applies to the laboratory data in the "Other Pediatric Clinical Experience" category.

16. 4-Month Safety Update

This safety update is dated 4/14/00. It is listed as submission # 003 under NDA 21216.

16.1 Sources Of Data

This submission contains updated safety data from 2 broad overlapping sources

- Randomized controlled and open-label extension studies that are listed under the combined adjunctive therapy and monotherapy grouping above, and are also referred to by the sponsor as Pediatric Submission studies.
  - These studies are: 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95.
  - The only study included in the safety update that contributes safety data beyond that included in the original NDA 21216 submission of 12/14/99 is Study 945-301/401.

- Summaries of deaths, serious adverse events and adverse event dropouts for the Pediatric Submission studies as well as studies listed as "Approved NDA Pediatric Experience" and "Other Pediatric Clinical Experience"

Data omitted from the safety update include the following:

- Safety data from the 2 clinical pharmacology studies 945-202 and 945-296 are omitted from the safety update: all safety data for these studies have already been summarized in Section 8.
- Safety data from studies listed as "Approved NDA Pediatric Experience" and "Other Pediatric Clinical Experience" are not included in the safety update with the exception of summaries of deaths, serious adverse events and adverse event dropouts.

16.2 Number Of Patients Included In Safety Update

Safety data in the update for the combined adjunctive therapy and monotherapy studies, also referred to by the sponsor as the pediatric submission studies (945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95) are for a cumulative total of 648 individual gabapentin-treated patients, ages 1 month to 12 years; 597 individual gabapentin-treated patients were included in the original NDA 21216 submission. Although study 945-301/401 is technically an open-label extension to Study 945-305/405, patients could enter Study 945-301/401 without having participated in Study 945-305/405.

Deaths, serious adverse events and adverse event discontinuations are for a total denominator of 696 gabapentin-treated patients in the age range 1 month to 12 years.

The following sponsor-provided table summarizes the overall origin of patients in the original NDA 21216 submission and safety update (the sponsor has referred to the current update as Safety Update 1)

Origin of Patients From All Clinical Studies in ISS and SU1		
	Number of GBP-Treated Patients	
Includes Data From:	ISS	SU1
Pediatric Submission Studies	597	648
Approved NDA Studies	42	42
Other Pediatric Experience	6	6
Total	645	696
GBP = gabapentin SU1 = Safety Update 1		

The next table which has also been provided by the sponsor summarizes the origin of patients in the original NDA 21216 submission and safety update in reference to specific studies in the Pediatric Submission Studies group

Origin of Patients From Pediatric Submission Studies in ISS and SU1				
	Total Number of GBP-Treated Patients		First-Time GBP Exposures	
Includes Combined Data From Pediatric Submission Studies:	ISS	SU1	ISS	SU1
945-305/405 Double-Blind	38	38	38	38
945-301/401 Open-Label	145	198	110	161
945-86/186 Double-Blind	119	119	119	119

945-87/187 Open-Label	237	237		125	125
945-94 Double-Blind	113	113		113	113
945-95 Open-Label	191	191		92	92
Total Gabapentin Exposures:				597	648

GBP = gabapentin
SU1 = Safety Update 1

From the above table it can be seen that the population (i.e., denominator) that is newly covered in the safety update, and was not included in the original NDA Integrated Summary of Safety, comprises 53 gabapentin-treated patients drawn from the open-label study 945-301/401.

16.3 Cut-Off Dates

The cut-off dates for the original NDA 21216 submission and safety update are in the following table, provided by the sponsor.

Cut-off Dates for Gabapentin Pediatric sNDA and SU1			
	Submission Date	Safety Database	Serious Adverse Events and Deaths[a]
sNDA	December 14, 1999	August 13, 1999 (ISS Database)	November 10, 1999
SU1	April 14, 2000	December 31, 1999 (SU1 Database)	February 14, 2000

[a] Includes all serious adverse events and deaths reported to Parke-Davis Clinical Safety database by specified date.
sNDA = Original NDA 21216 submission
SU1 = Safety Update 1

16.4 Pediatric Submission Studies

16.4.1 Demographics

The demographics for the safety update are similar to those for the original Integrated Summary of Safety as indicated in the following table, provided by the sponsor.

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Characteristics of Gabapentin-Treated Patients: Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95				
Characteristic	ISS N = 597		SU1 N = 648	
Sex, N (%)				
Male	333	(55.8)	352	(54.3)
Female	264	(44.2)	296	(45.7)
Age, years				
N	597		648	
Mean (SD)	6.8	(3.5)	6.5	(3.6)
Median	7.0		7.0	
Range	0.2-13.0		0.2-13.0	
Race, N (%)				
White	474	(79.4)	512	(79.0)
Black	55	(9.2)	62	(9.6)
Hispanic	27	(4.5)	32	(4.9)
Asian	12	(2.0)	12	(1.9)
American Indian	1	(0.2)	1	(0.2)
Other	28	(4.7)	29	(4.5)
Weight, kg				
N	597		648	
Mean (SD)	27.6	(14.1)	26.4	(14.3)
Median	25.9		24.7	
Range	3.0-101.8		3.0-101.8	
Height, cm				
N	580		624	
Mean (SD)	120.2	(25.4)	117.6	(26.5)
Median	125.1		123.0	
Range	47.5-175.3		47.5-175.3	
Duration of Epilepsy, years				
N	597		648	
Mean (SD)	3.0	(3.1)	2.8	(3.0)
Median	1.8		1.6	
Range	<1-11.9		<1-11.9	
Concurrent AEDs, N (%)				
0	137	(22.9)	164	(25.3)
1	201	(33.7)	209	(32.3)
2	169	(28.3)	177	(27.3)
3	84	(14.1)	92	(14.2)
4	6	(1.0)	6	(0.9)
AED = Antiepileptic Drug; SD = Standard Deviation.				

16.4.2 Exposure Data

These are summarized in the next table, provided by the sponsor; total exposure to gabapentin has been increased to 474.5 patient-years with the submission of the Safety Update

Duration of Exposure to Gabapentin: Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95				
	Cumulative Number (%) of Patients			
Duration of Exposure[a]	ISS N = 597		SU1 N = 648	
≥ 1 Dose	594[b]	(99.5)	645[b]	(99.5)
≥ 1 Week	571	(95.6)	642	(99.1)
≥ 2 Weeks	562	(94.1)	637	(98.3)
≥ 4 Weeks	531	(88.9)	625	(96.5)
≥ 6 Weeks	480	(80.4)	611	(94.3)
≥ 8 Weeks	466	(78.1)	600	(92.6)
≥ 10 Weeks	436	(73.0)	579	(89.4)
≥ 12 Weeks	424	(71.0)	552	(85.2)
≥ 14 Weeks	402	(67.3)	477	(73.6)
≥ 16 Weeks	389	(65.2)	447	(69.0)
≥ 18 Weeks	383	(64.2)	427	(65.9)
≥ 20 Weeks	377	(63.1)	414	(63.9)
≥ 22 Weeks	364	(61.0)	398	(61.4)
≥ 24 Weeks	341	(57.1)	368	(56.8)
≥ 26 Weeks	301	(50.4)	316	(48.8)
≥ 28 Weeks	271	(45.4)	274	(42.3)
≥ 30 Weeks	261	(43.7)	263	(40.6)
≥ 32 Weeks	256	(42.9)	257	(39.7)
≥ 34 Weeks	251	(42.0)	251	(38.7)
≥ 36 Weeks	237	(39.7)	237	(36.6)
≥ 38 Weeks	197	(33.0)	197	(30.4)
≥ 40 Weeks	171	(28.6)	171	(26.4)
≥ 42 Weeks	160	(26.8)	160	(24.7)
≥ 44 Weeks	158	(26.5)	158	(24.4)
≥ 46 Weeks	158	(26.5)	158	(24.4)
≥ 48 Weeks	152	(25.5)	152	(23.5)
≥ 50 Weeks	150	(25.1)	150	(23.1)
≥ 52 Weeks	146	(24.5)	146	(22.5)
≥ 56 Weeks	143	(24.0)	143	(22.1)
≥ 60 Weeks	139	(23.3)	139	(21.5)
≥ 64 Weeks	133	(22.3)	133	(20.5)
≥ 68 Weeks	124	(20.8)	124	(19.1)
≥ 72 Weeks	120	(20.1)	120	(18.5)
≥ 76 Weeks	114	(19.1)	114	(17.6)
≥ 80 Weeks	109	(18.3)	109	(16.8)
≥ 84 Weeks	101	(16.9)	101	(15.6)
≥ 88 Weeks	90	(15.1)	90	(13.9)
≥ 92 Weeks	85	(14.2)	85	(13.1)
≥ 96 Weeks	76	(12.7)	76	(11.7)
≥ 100 Weeks	60	(10.1)	60	(9.3)
≥ 104 Weeks	47	(7.9)	47	(7.3)
≥ 112 Weeks	28	(4.7)	28	(4.3)
≥ 120 Weeks	18	(3.0)	18	(2.8)
Total Patient-Days	158793.0		173315.0	
Total Patient-Weeks	22684.7		24759.3	
Total Patient-Years	434.8		474.5	

[a] Includes days on which gabapentin dosing was briefly interrupted (gabapentin dose = 0 mg).
[b] Excludes 3 patients from Study 945-95: Patient 2 (Center 49) and Patient 2 (Center 66) because of missing dosing records, and Patient 4 (Center 34) because of a total daily dose entry of zero.

16.4.3 Maximum Dose Received

The maximum dose of gabapentin received in this group of studies is summarized in the following (sponsor's) table

Dosage Summary for Gabapentin-Treated Patients			
Dosage (mg/kg/day)	Study 945-305/405[a]	Study 945-301/401[b]	All Pediatric Submission Studies[c]
	N = 38	N = 198	N = 648
Maximum Dose Received by Patient			
N	38	198	645[d]
Mean (SD)	42.81 (14.15)	51.59 (11.56)	42.66 (14.81)
Median	40.99	50.00	39.41
Range	34.62–128.57	13.25–78.13	5.95–128.57

[a] Protocol-specified target dosage was 40 mg/kg/day.
[b] Protocol-specified target dosage was 40 to 60 mg/kg/day.
[c] Includes Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95.
[d] Excludes 3 patients from Study 945-95: Patient 2 (Center 49) and Patient 2 (Center 66) because of missing dosing records, and Patient 4 (Center 34) because of a total daily dose entry of zero.

16.4.4 Overview Of Adverse Events

An overview of all adverse events for the pediatric submissions grouping is presented in the following table, provided by the sponsor.

Overview of Adverse Events in Gabapentin-Treated Patients: Pediatric Submission Studies 945-305/405, 945-301/401, 945-86/186, 945-87/187, 945-94, and 945-95				
	ISS N = 597		SU1 N = 648	
Number (%) of Patients With TESS AEs				
All AEs	466	(78.1)	552	(85.2)
Associated AEs[a]	240	(40.2)	274	(42.3)
Number (%) of Patients With TESS AEs by Gender				
All AEs				
Males	274/333	(82.3)	309/352	(87.8)
Females	192/264	(72.7)	243/296	(82.1)
Associated AEs[a]				
Males	133/333	(39.9)	152/352	(43.2)
Females	107/264	(40.5)	122/296	(41.2)
Number (%) of Patients With TESS AEs by Maximum Intensity				
All AEs				
Mild	209	(35.0)	237	(36.6)
Moderate	211	(35.3)	249	(38.4)
Severe	45	(7.5)	65	(10.0)
Associated AEs[a]				
Mild	126	(21.1)	146	(22.5)
Moderate	89	(14.9)	101	(15.6)
Severe	24	(4.0)	27	(4.2)
Number of Deaths	0[b]		1[c]	(0.2)
Number (%) of Patients With Serious AEs	45	(7.5)	74	(11.4)
Number (%) of Patients Withdrawn Due to AEs				
All AEs	32	(5.4)	38	(5.9)
Associated AEs[a]	31	(5.2)	35	(5.4)

[a] Adverse events the investigator considered definitely, probably, or possibly related to study medication, and events for which there was insufficient information to make a determination of relationship.
[b] The ISS database contained no patient deaths; however, one patient in the ongoing gabapentin open-label study (945-301/401) died after the August 13, 1999, cut-off date for the ISS database. For completeness, details of this death were included in the ISS. This death is contained in the SU1 database.
[c] A second patient in the ongoing Study 945-301/401 has died, but the death occurred after the December 31, 1999, data cut-off date for the SU1 database. However, for completeness of reporting, this death is described in this safety update.

As the above table indicates the overall incidence of adverse events, severe adverse events, and serious adverse events increased slightly in the Safety

Update as compared with the Integrated Summary of Safety. Also note the footnotes in the table regarding the 2 patient deaths in the entire safety database

16.4.5 Frequent Adverse Events

Adverse events occurring in ≥ 2% of patients are summarized in the next sponsor-provided table. These adverse events are not substantially different from those in the Integrated Summary of Safety. In addition most of the highest-frequency adverse events can be attributed to concurrent upper respiratory infections.

Adverse Events (≥2% of Gabapentin-Treated Patients) by Decreasing Frequency[a]: Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95

[Number (%) of Patients]

Preferred Term	ISS N = 597		SU1 N = 648	
Rhinitis	82	(13.7)	107	(16.5)
Somnolence	78	(13.1)	107	(16.5)
Fever	68	(11.4)	106	(16.4)
Upper Respiratory Infection	77	(12.9)	104	(16.0)
Pharyngitis	88	(14.7)	99	(15.3)
Viral Infection	77	(12.9)	92	(14.2)
Headache	82	(13.7)	85	(13.1)
Nausea and/or Vomiting	61	(10.2)	72	(11.1)
Otitis Media	39	(6.5)	55	(8.5)
Coughing	35	(5.9)	49	(7.6)
Emotional Lability	42	(7.0)	44	(6.8)
Rash	36	(6.0)	42	(6.5)
Diarrhea	30	(5.0)	41	(6.3)
Abdominal Pain	35	(5.9)	36	(5.6)
Nervousness	23	(3.9)	35	(5.4)
Sinusitis	26	(4.4)	33	(5.1)
Hostility	28	(4.7)	30	(4.6)
Bronchitis	21	(3.5)	27	(4.2)
Hyperkinesia	25	(4.2)	27	(4.2)
Dizziness	26	(4.4)	26	(4.0)
Inner Ear Infection	19	(3.2)	26	(4.0)
Ataxia	17	(2.8)	24	(3.7)
Pneumonia	9	(1.5)	24	(3.7)
Insomnia	18	(3.0)	23	(3.5)
Fatigue	22	(3.7)	22	(3.4)
Weight Increase	20	(3.4)	21	(3.2)
Anorexia	15	(2.5)	20	(3.1)
Fracture	19	(3.2)	20	(3.1)
Convulsions	19	(3.2)	19	(2.9)
Gastroenteritis	16	(2.7)	19	(2.9)
Myalgia	16	(2.7)	18	(2.8)
Thinking Abnormal	17	(2.8)	18	(2.8)
Conjunctivitis	11	(1.8)	17	(2.6)
Dyspepsia	14	(2.3)	15	(2.3)
Epistaxis	12	(2.0)	15	(2.3)
Increased Appetite	13	(2.2)	15	(2.3)
Dental Abnormalities	8	(1.3)	13	(2.0)
Skin Laceration	12	(2.0)	13	(2.0)
Urinary Incontinence	12	(2.0)	13	(2.0)
Any Adverse Event	466	(78.1)	552	(85.2)

[a] Sorted by decreasing frequency on the basis of data in SU1 column.

16.4.6 Clinical Laboratory Data

The incidence of very low and very high laboratory values in patients in the Integrated Summary of Safety and in the Pediatric Submission Studies grouping in the Safety Update are summarized in the attached sponsor-provided table.

Gabapentin-Treated Patients With Very Low or Very High Clinical Laboratory Values in Pediatric Submission Studies 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95
[Number (%) of Patients][a]

	ISS					SU1				
Parameter	N	Very Low		Very High		N	Very Low		Very High	
Hemoglobin	542	0	(0.0)	1	(0.2)	610	0	(0.0)	1	(0.2)
Hematocrit	542	0	(0.0)	1	(0.2)	610	0	(0.0)	1	(0.2)
Red Blood Cells	542	0	(0.0)	1	(0.2)	610	0	(0.0)	1	(0.2)
Platelets	541	6	(1.1)	7	(1.3)	609	9	(1.5)	13	(2.1)
White Blood Cells	542	5	(0.9)	6	(1.1)	610	5	(0.8)	16	(2.6)
Neutrophils	538	26	(4.8)			610	29	(4.8)		
BUN	544			1	(0.2)	613			1	(0.2)
Uric Acid	124			0	(0.0)	193			1	(0.5)
Potassium	542			1	(0.2)	611			3	(0.5)
Chloride	544			1	(0.2)	613			1	(0.2)
Glucose	538	2	(0.4)	1	(0.2)	607	3	(0.5)	1	(0.2)
Amylase	124			2	(1.6)	193			8[b]	(4.1)
SGPT	543			0	(0.0)	612			1	(0.2)

Note: Cells with missing information do not have sponsor-defined ranges.
[a] Percent based on N for individual parameter.
[b] Three very high values in the SU1 database are not abnormal by the range of normals for the local lab (Fleury) in Brazil that performed the assays. These 3 values are not shown in this table.

The sponsor's criteria for very high and very low laboratory values for the parameters listed in the above table are below (sponsor-provided table)

Parameter	Very Low		Very High	
Age Range	< 2 years	2-12 years	< 2 years	2-12 years
Hemoglobin	≤ 7.0	≤ 6.0	≥ 20	≥ 21
Hematocrit	≤ 20	≤ 24	≥ 50	≥ 54
RBC	≤ 2.1	≤ 2.2	≥ 6.0	≥ 7.6
Platelets	≤ 100	≤ 100	≥ 600	≥ 600
White Blood Cells	≤ 2.667	≤ 2.667	≥ 25	≥ 15
Neutrophils	≤ 1.0	≤ 1.0		
BUN			≥ 17.9	≥ 17.9
Potassium			≥ 7.0	≥ 7.0
Chloride			≥ 122	≥ 122
Glucose	≤ 2.2	≤ 2.2	≥ 22.2	≥ 22.2
Amylase			≥ 120	≥ 500
Uric Acid			≥ 9.0	≥ 10.7
SGPT			≥ 300	≥ 300

Units for the above parameters are in the next table, also provided by the sponsor.

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Parameter	Units
Hemoglobin	G/dL
Hematocrit	%
RBC	X 10^{12}/L
Platelets	X 10^{9}/L
White Blood Cells	X 10^{3}/μL
Neutrophils	X 10^{3}/μL
BUN	mmol/L
Potassium	mEq/L
Chloride	mEq/L
Glucose	mmol/L
Amylase	U/L
Uric Acid	mg/dL
SGPT	U/L

In regard to the laboratory data presented in the above table the following are of note:

- Of the 3 additional cases of very low neutrophil counts (i.e., not reported in the Integrated Summary of Safety) none were less than 500 x 10^{3}/μL and therefore not considered to be severe
- Of the 6 additional cases with a very high serum amylase (3 were reported in the Pediatric Submission Studies included in the Integrated Summary of Safety)
  - 4 were either isolated or the result of concurrent medical problems
  - One was in a patient in whom the baseline reading was slightly elevated and whose amylase rose slightly during treatment without any concurrent gastrointestinal signs
  - One was in a patient in whom the amylase value at screening was already very high, rose further on gabapentin while having a fever and then returned to normal even while gabapentin was continued
- One patient had a very high SGPT. This patient (# 019504 participating in Study # 945-301/401) had hepatosplenomegaly at initial evaluation and, at screening, had values for SGPT ([redacted]), SGOT ([redacted]), and alkaline phosphatase ([redacted]) above normal range. One month after the start of open-label medication, the patient had a very high SGPT value of [redacted] with SGOT higher than at screening ([redacted]) and alkaline phosphatase slightly lower ([redacted]). In subsequent visits, and while continuing medication, all 3 enzyme values declined but not to normal, the patient had an SGPT of [redacted], SGOT of [redacted], and alkaline phosphatase of [redacted]. 3 months after the start of open-label medication. In January 2000 a liver biopsy was negative. The investigator reports that the patient had an underlying metabolic disorder that was responsible for the liver dysfunction, probably a syndrome such as Zellweger's.
- 3 patients had thrombocytopenia: in 2 patients this was attributed to a specimen of blood that clotted and in a third the platelet count rose when the dose of valproic acid was decreased
- According to the sponsor: All other very low and very high values in the safety update not already reported in the Integrated Summary of Safety either resulted from preexisting medical conditions, from acute infections, or were sporadic, isolated values not associated with adverse events or other laboratory abnormalities.

Since none of the above laboratory abnormalities, was associated with deaths, serious adverse events or adverse event dropouts, detailed narratives and Case Report Forms for these patients have not been provided by the sponsor

16.5 Deaths

2 deaths have occurred in all pediatric clinical studies of gabapentin; one of these was already described in the Integrated Summary of Safety (Patient # 075501 participating in Study 945-301)

The second death is described below

Patient 035501, was a 23-month-old female with partial seizures participating in Study 945-301. Her medical history included left-sided cerebral palsy, hypotonia, gastroesophageal reflux, and intractable seizures. Study medication consisted of 3 days of double-blind placebo treatment, followed by open-label gabapentin for 4 days at 375 mg/day, 16 days at 300 mg/day, 15 days at 375 mg/day, 63 days at 450 mg/day, 91 days at 525 mg/day, and 29 days at 600 mg/day, for a total exposure of 218 days. Concomitant medications included carbamazepine, clonazepam, lamotrigine, valproic acid, and levocarnitine. The patient's mental status and overall functioning gradually deteriorated, over the course of the study, in a manner believed to have been consistent with an underlying epileptic encephalopathy, whose etiology remained unknown in spite of extensive diagnostic evaluation. The patient became comatose on Study Day 218 while under the care of her primary care physician, with no precipitating factors known to the investigator. The family elected to keep the patient at home. Study medication was continued. On Study Day 221, the patient awoke from coma, had an increase in seizure activity, and appeared to be in pain. Morphine was prescribed in standard doses for comfort. On Study Day 222, the patient died. The investigator considered the epileptic encephalopathy to be profound and the adverse event to be severe in intensity and definitely not related to study medication.

Note that this death occurred after the cut-off date for the Safety Update.

16.6 Serious Adverse Events

Serious adverse events that occurred in any clinical study of gabapentin at the time of the original submission and at the time of the safety update are in the following sponsor-provided table

Summary of Serious Adverse Events That Occurred in Any Pediatric Patient Receiving Gabapentin During a Clinical Study [Number (%) of Patients]

Body System/ Preferred Term	ISS N = 645 To August 13, 1999		SU1 N = 696 To December 31, 1999	
None	594	(92.1)	616	(88.5)
Respiratory System	**17**	**(2.6)**	**34**	**(4.9)**
Pneumonia	6	(0.8)	16	(2.3)
Respiratory Distress	3	(0.5)	8	(1.1)
Upper Respiratory Infection	3	(0.5)	6	(0.9)
Aspiration Pneumonia	1	(0.2)	4	(0.6)
Asthma	2	(0.3)	3	(0.4)
Pharyngitis	2	(0.3)	2	(0.3)
Abscess, Peritonsillar	1	(0.2)	1	(0.1)
Apnea	0	(0.0)	1	(0.1)
Lung Disease	0	(0.0)	1	(0.1)
Pleural Disorder	0	(0.0)	1	(0.1)
Respiratory Infection	2	(0.3)	1	(0.1)
Body As A Whole	**15**	**(2.3)**	**25**	**(3.6)**
Dehydration	2	(0.3)	7	(1.0)
Fever	3	(0.5)	7	(1.0)
Drug Overdose	5	(0.8)	5	(0.7)
Viral Infection	3	(0.5)	3	(0.4)
Drug Toxicity	1	(0.2)	2	(0.3)
Sepsis	1	(0.2)	2	(0.3)

Headache	1	(0.2)	1	(0.1)
Injury, Accidental	1	(0.2)	1	(0.1)
Salmonella	1	(0.2)	1	(0.1)
Nervous System	**14**	**(2.2)**	**15**	**(2.2)**
Convulsions	7	(1.1)	7	(1.0)
Somnolence	3	(0.5)	3	(0.4)
Ataxia	1	(0.2)	2	(0.3)
Confusion	2	(0.3)	2	(0.3)
Stupor	2	(0.3)	2	(0.3)
Hemiplegia	1	(0.2)	1	(0.1)
Intracranial Hypertension	1	(0.2)	1	(0.1)
Shunt Failure	1	(0.2)	1	(0.1)
Digestive System	**6**	**(0.9)**	**12**	**(1.7)**
Nausea and/or Vomiting	3	(0.5)	5	(0.7)
Appendicitis	2	(0.3)	2	(0.3)
Gastroenteritis	0	(0.0)	2	(0.3)
Abdominal Pain	1	(0.2)	1	(0.1)
Anorexia	0	(0.0)	1	(0.1)
Esophagitis	0	(0.0)	1	(0.1)
Skin and Appendages	**5**	**(0.8)**	**6**	**(0.9)**
Animal Bite	1	(0.2)	1	(0.1)
Contusion	1	(0.2)	1	(0.1)
Insect/Bug Bites	1	(0.2)	1	(0.1)
Mycotic Infection	0	(0.0)	1	(0.1)
Pruritic Rash	1	(0.2)	1	(0.1)
Skin Infection	1	(0.2)	1	(0.1)
Cardiovascular System	**2**	**(0.3)**	**5**	**(0.7)**
Cardiorespiratory Failure	0	(0.0)	1	(0.1)
Heart Failure	0	(0.0)	1	(0.1)
Hemorrhage	0	(0.0)	1	(0.0)
Tachycardia	1	(0.2)	1	(0.1)
Thrombosis	1	(0.2)	1	(0.1)
Musculoskeletal System	**4**	**(0.7)**	**4**	**(0.6)**
Fracture	4	(0.7)	4	(0.6)
Psychobiologic Function	4	(0.7)	4	(0.6)
Hostility	2	(0.3)	2	(0.3)
Emotional Lability	1	(0.2)	1	(0.1)
Hysteria	1	(0.2)	1	(0.1)
Suicidal	1	(0.2)	1	(0.1)
Special Senses	**2**	**(0.3)**	**4**	**(0.6)**
Otitis Media	2	(0.3)	4	(0.6)
Laboratory Deviations	**1**	**(0.2)**	**3**	**(0.4)**
Hematuria	1	(0.2)	2	(0.3)
Granulocytopenia	0	(0.0)	1	(0.1)
Urogenital System	**2**	**(0.3)**	**3**	**(0.4)**
Urinary Tract Infection	1	(0.2)	2	(0.3)
Urinary Incontinence	1	(0.2)	1	(0.1)
Hemic and Lymphatic	**0**	**(0.0)**	**2**	**(0.3)**
Purpura	0	(0.0)	1	(0.1)
Thrombocytopenia	0	(0.0)	1	(0.1)
Metabolic and Nutritional Disorders	**1**	**(0.2)**	**1**	**(0.1)**
Metabolic Disorder	1	(0.2)	1	(0.1)
Any Serious Adverse Event	**51**	**(7.9)**	**80**	**(11.5)**

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Serious adverse events that occurred in Protocol 945-301/401 after the cut-off date for the safety update are summarized in the following table, provided by the sponsor.

Summary of Serious, Nonfatal Adverse Events That Occurred in Ongoing, Open-Label Gabapentin Extension Study 945-301/401 During the Period of January 1, 2000 to February 14, 2000[a] (Number of Patients)	
Body System/ Preferred Term	Gabapentin
Respiratory System	**8**
Pneumonia	3
Bronchitis	1
Respiratory Distress	1
Respiratory Infection	1
Rhinitis	1
Upper Respiratory Infection	1
Nervous System	**3**
Nervousness	1
Somnolence	1
Body As A Whole	**2**
Dehydration	1
Fever	1
Digestive System	**1**
Hepatic Failure	1
Skin and Appendages	**1**
Skin Disorder	1
Urogenital System	**1**
Urinary Tract Infection	1
Any Serious Adverse Event	**14**
[a]These serious adverse events were reported to the Parke-Davis Clinical Safety database after the December 31, 1999 cut-off date for the SU1 database.	

Based on the above tables for serious adverse events, 2 patients are described further

Patient # 038001 participating in Study 945-301 had hepatic failure ("acute toxic hepatitis") listed as a serious adverse event. This patient was a girl who was 41 months old at the time of study entry; she had not participated in a preceding double-blind study. She had a past history of Foix-Chavany-Marie syndrome, bilateral ear-tube insertions, persistent cough and difficulty swallowing. Concomitant medication included carbamazepine. From the 3rd to 5th week of the study she required treatment for a pneumonia accompanied by status epilepticus. On Study Day 165 of open-label gabapentin, the patient was hospitalized for fever, cough, and status epilepticus. At that time she had received gabapentin in a dose of 525 mg/day for 13 days followed by 675 mg/day for 152 days. AST and ALT (5768 and 5726 u/L, respectively), carbamazepine (33 µg/mL), and lipase (533 u/L) levels were markedly elevated. While the seizures were successfully treated, the patient remained in coma; hypoxic-ischemic brain injury secondary to status epilepticus, hepatic failure and pancreatitis were diagnosed. Carbamazepine was discontinued and the patient recovered from the acute hepatitis and pancreatitis, her transaminase and lipase readings returning to normal or close-to-normal (< 2 x upper limit of normal). At the most recent assessment (Day 355) the patient had a tracheostomy, gastrojejunostomy tube emplacement, and neurological sequelae including a depressed level of cognition, spasticity and choreoathetosis. Gabapentin was continued throughout the illness; in addition phenobarbital was used to control her seizures.

Reviewer's note:

- *It is extremely unlikely that gabapentin was responsible for her syndrome of hepatitis and pancreatitis, especially since these conditions resolved despite the continuation of gabapentin*
- *Foix-Chavany-Marie syndrome refers to a supranuclear bulbar palsy caused by bilateral anterior opercular lesions and involving facial, masticatory, lingual, palatopharyngeal and laryngeal muscles. In this particular patient the syndrome was believed to have been caused by a cortical dysplasia involving both opercular regions, and seen on MRI*

Patient # 201501 participating in Study 945-401 had thrombocytopenia and granulocytopenia, listed as a serious adverse event. The patient was a 7-month old girl with mental retardation, cerebral dysgenesis, microcephaly, craniosynostosis, bulbar palsy, recurrent aspiration and seizures. Concomitant medications

included valproic acid, clonazepam and phenobarbital. She had not participated in a preceding double-blind study. On Day 31 she was detected to have thrombocytopenia with a platelet count of [redacted]; at that time she was receiving gabapentin 37.5 mg/kg and valproate 40 mg/kg; her gabapentin dose subsequently varied slightly and her valproate dose was reduced. Beginning Day 58 she developed a pneumonia that required ventilatory support and treatment with antibiotics. On Day 66 valproate was discontinued after her platelet count was noted to be [redacted]; she was treated with fresh frozen plasma, factor VIII, Vitamin K and platelet transfusions. On Day 93 examination of a bone marrow aspirate showed normal myeloid and erythroid cell lines. On Day 93 her platelet count was [redacted]. However on Day 96 she had an absolute neutrophil count of [redacted] and was treated with granulocyte-colony-stimulating-factor; her neutrophil count is described as being normal the next day and she was considered to have a cyclical neutropenia. On Days 184-187 her counts were as follows: platelets [redacted]; neutrophils [redacted] Gabapentin was continued throughout. A tabular summary of serial hematocrit, neutrophil count and platelet count values is below.

Study Days	Hematocrit %	Neutrophils X 10^9/L	Platelets X 10^9/L
1/ 4	34.7	[redacted]	
31/ 34	29.3		
62/ 65	61.3		
93/ 96	35.1		
184/ 187	42.3		

Reviewer's note: It is unlikely that gabapentin was responsible for her thrombocytopenia and granulocytopenia, especially since these laboratory abnormalities resolved and remained normal 3 further months later, despite the continuation of gabapentin.

16.7 Discontinuations Due To Adverse Events

16.7.1 Overview

Withdrawals due to adverse events across all pediatric studies are summarized in the following sponsor-provided table

	Cumulative Number (%) of Patients			
Withdrawals Due to Adverse Events	ISS		SU1	
Pediatric Submission Studies[a] 945-86/186, 945-87/187, 945-305/405, 945-301/401, 945-94, and 945-95	32/597	(5.4)	38/648	(5.9)
Approved NDA Studies (945-11, 945-11X, 945-16, 945-19, 945-19X, 945-49, 945-20, 945-20X, 945-50, 877-034, and 877-034X) and 945-08	6/48	(12.5)	6/48	(12.5)
All Pediatric Clinical Experience (Pediatric Submission Studies, Approved NDA Studies, and 945-08 Combined)	38/645	(5.9)	44/696	(6.3)

[a]Patients who withdrew from gabapentin treatment in both double-blind and open-label studies were counted once. Includes only withdrawals due to treatment-emergent signs and symptoms.

16.7.2 Specific Adverse Events Leading To Treatment Withdrawal

These are outlined in the next sponsor-submitted table and do not indicate any items of special concern, or major differences from the data submitted with the Integrated Summary of Safety

Withdrawals Due to Adverse Events for All Pediatric Clinical Experience [Number (%) of Patients]				
	Gabapentin			
Body System/ Preferred Term	ISS N = 645		SU1 N = 696	
None	607	(94.1)	652	(93.7)
Psychobiologic Function	**16**	**(2.5)**	**18**	**(2.6)**
Emotional Lability	8	(1.2)	8	(1.1)
Hostility	6	(0.9)	7	(1.0)
Thinking Abnormal	3	(0.5)	3	(0.4)
Nervousness	1	(0.2)	2	(0.3)
Personality Disorder	2	(0.3)	2	(0.3)
Agitation	1	(0.2)	1	(0.1)

Anxiety	1	(0.2)	1	(0.1)
Apathy	1	(0.2)	1	(0.1)
Nervous System	**17**	**(2.6)**	**17**	**(2.4)**
Convulsions	8	(1.2)	8	(1.1)
Hyperkinesia	6	(0.9)	6	(0.9)
Somnolence	4	(0.6)	4	(0.6)
Ataxia	2	(0.3)	2	(0.3)
Confusion	2	(0.3)	2	(0.3)
Insomnia	2	(0.3)	2	(0.3)
Amnesia	1	(0.2)	1	(0.1)
Coordination Abnormal	1	(0.2)	1	(0.1)
Speech Disorder	1	(0.2)	1	(0.1)
Stupor	1	(0.2)	1	(0.1)
Tremor	1	(0.2)	1	(0.1)
Body As A Whole	**7**	**(1.1)**	**8**	**(1.1)**
Fatigue	2	(0.3)	2	(0.3)
Drug Toxicity	1	(0.2)	1	(0.1)
Fever	0	(0.0)	1	(0.1)
Infectious Mononucleosis	1	(0.2)	1	(0.1)
Pain	1	(0.2)	1	(0.1)
Weight Decrease	1	(0.2)	1	(0.1)
Weight Increase	1	(0.2)	1	(0.1)
Digestive System	**6**	**(0.9)**	**8**	**(1.1)**
Anorexia	2	(0.3)	2	(0.3)
Increased Appetite	2	(0.3)	2	(0.3)
Nausea and/or Vomiting	1	(0.2)	2	(0.3)
Abdominal Pain	1	(0.2)	1	(0.1)
Diarrhea	1	(0.2)	1	(0.1)
Esophagitis	0	(0.0)	1	(0.1)
Gastroenteritis	1	(0.2)	1	(0.1)
Skin and Appendages	**2**	**(0.3)**	**2**	**(0.3)**
Sweating Increased	1	(0.2)	1	(0.1)
Urticaria	1	(0.2)	1	(0.1)
Urogenital System	**2**	**(0.3)**	**2**	**(0.3)**
Urinary Incontinence	2	(0.3)	2	(0.3)
Cardiovascular System	**1**	**(0.2)**	**1**	**(0.1)**
Heart Block	1	(0.2)	1	(0.1)
Special Senses	**0**	**(0.0)**	**1**	**(0.1)**
Eye Disorder	0	(0.0)	1	(0.1)
Any Adverse Event	38	(5.9)	44	(6.3)

16.8 Narratives For Deaths, Serious Adverse Events And Adverse Event Dropouts

I have read through all narratives for the above additional deaths, serious adverse events and adverse event dropouts, and supplemented the narratives with Case Report Forms when needed.

The narratives indicated that virtually all patients had serious concomitant illnesses. The spectrum of such illnesses included, but was not limited to, multiple congenital anomalies, cerebral palsy, inborn errors of metabolism, phakomatoses, and recurrent pneumonia and other infections.

There was no persuasive evidence from the narratives for a plausible causal role for gabapentin in any of the additional deaths, serious adverse events or adverse event discontinuations in the Safety Update (i.e., those not included in the Integrated Summary of Safety)

17. "Behavioral" Adverse Events In Pediatric Submission Studies

17.1 Background

An overview of adverse event tables from randomized controlled trials in an earlier section of this review appeared to indicate that some adverse events consistent with abnormalities of behavior were more common in those treated with gabapentin than in those treated with placebo. Similar adverse events also appeared to occur in open-label studies. Since similar symptoms could be associated with partial seizures themselves, and with a variety of underlying brain lesions, as well as possibly with medications other than gabapentin, I have attempted a more detailed analysis of such events. They include:

- A comprehensive tabulation of such adverse events in the 3 main randomized, double-blind, placebo-controlled trials included in this submission,
- A tabular listing of all serious behavioral adverse events and discontinuations due to behavioral adverse events in the pediatric submission studies

I have chosen a constellation of treatment-emergent adverse events that could suggest abnormal behavior. The preferred terms chosen for this analysis include emotional lability, hostility, hyperkinesia, thinking abnormal, psychiatric disorder, personality disorder, anxiety, agitation, nervousness, confusion, somnolence, stupor, insomnia, sleep disorder, speech disorder, suicidal, hallucination, dreaming abnormal, amnesia

17.2 Behavioral Adverse Events In Randomized, Double-Blind, Placebo-Controlled Trials

The clinical trials included in this section are:

- Randomized, double-blind, placebo-controlled, adjunctive-therapy trials
  945-86/186
  945-305/405
- Randomized, double-blind, placebo-controlled monotherapy trials
  945-94

17.2.1 All Adverse Events

17.2.1.1 Behavioral Adverse Events In Study # 945-86/186

These are summarized in the next table, adapted from one provided by the sponsor. As the table indicates, hostility and emotional lability may have been particularly common in those treated with gabapentin as compared with those who received placebo.

	Placebo (n=128)		Gabapentin (n=119)	
Preferred Term	N	%	N	%
Hyperkinesia	1	0.8	3	2.5
Insomnia	1	0.8	3	2.5
Hostility	3	2.3	9	7.6
Emotional Lability	2	1.6	5	4.2
Nervousness	1	0.8	2	1.7
Personality Disorder	0	0	2	1.7
Thinking Abnormal	0	0	1	0.8

Agitation	1	0.8	1	0.8
Psychiatric Disorder	0	0	1	0.8
Somnolence	6	4.7	10	8.4
Stupor	0	0	1	0.8
Confusion	1	0.8	1	0.8
Sleep Disorder	1	0.8	0	0

Line listings are provided by the sponsor for the above gabapentin- and placebo-treated patients with emotional lability, hostility, psychiatric disorder, hyperkinesia, personality disorder, and agitation. These line listings include the following information: study number, center and patient number, patient age and gender, gabapentin dose, investigator term, intensity, study day of onset, duration, relationship to study drug, management, outcome, other adverse events and pertinent history. The next table illustrates the number of these patients with a history suggestive of related behavioral abnormalities prior to study entry. From the table it appears that a majority of gabapentin-treated patients with hostility, emotional lability and hyperkinesia had related behavioral abnormalities prior to study entry

	Placebo (n=128)		Gabapentin (n=119)	
Preferred Term	Number of patients with adverse event	Number of patients with prior behavioral abnormalities related to adverse event	Number of patients with adverse event	Number of patients with prior behavioral abnormalities related to adverse event
Hyperkinesia	1	0	3	2
Hostility	3	1	9	5
Emotional Lability	2	2	5	3
Personality Disorder	0	0	2	1
Agitation	1	0	1	0
Psychiatric Disorder	0	0	1	0

17.2.1.2 Behavioral Adverse Events In Study # 945-305/405

There were no adverse events in the "behavioral" category recorded during this study, except for somnolence; this is not surprising given the age range of patients enrolled.

The incidence of somnolence in both treatment groups is as summarized in the following table derived from one provided by the sponsor; as the table indicates the incidence of somnolence was much higher in those treated with gabapentin than in those treated with placebo

	Placebo (n=38)		Gabapentin (n=38)	
Preferred Term	N	%	N	%
Somnolence	1	2.6	6	15.8

17.2.1.3 Behavioral Adverse Events In Study # 945-94

These are summarized in the next table, derived from one provided by the sponsor. As the table indicates, adverse events listed as "emotional lability" and "nervousness" appear to have the most common in this category among patients treated with gabapentin as compared with those treated with placebo.

	Placebo (n=112)		Gabapentin (n=113)	
Preferred Term	**N**	**%**	**N**	**%**
Hyperkinesia	7	6.3	8	7.1
Insomnia	5	4.5	4	3.5
Hostility	0	0	3	2.7
Emotional Lability	1	0.9	8	7.1
Personality Disorder	0	0	1	0.9
Thinking Abnormal	0	0	3	2.7
Anxiety	0	0	2	1.8
Suicidal	0	0	1	0.9
Hallucination	1	0.9	0	0
Nervousness	0	0	8	7.1
Somnolence	5	4.5	2	1.8
Confusion	1	0.9	0	0
Dreaming Abnormal	1	0.9	2	1.8
Speech Disorder	0	0	1	0.9
Amnesia	0	0	1	0.9

Line listings are provided by the sponsor for the above gabapentin- and placebo-treated patients with emotional lability, hostility, hyperkinesia, personality disorder, and suicidal. These line listings include the following information: study number, center and patient number, patient age and gender, gabapentin dose, investigator term, intensity, study day of onset, duration, relationship to study drug, management, outcome, other adverse events and pertinent history. The next table illustrates the number of these patients with a history suggestive of related behavioral abnormalities prior to study entry. From the table it appears that ≤ 50 % of gabapentin-treated patients with hostility, emotional lability and hyperkinesia had related behavioral abnormalities prior to study entry.

	Placebo (n=112)		Gabapentin (n=113)	
Preferred Term	Number of patients with adverse event	Number of patients with prior behavioral abnormalities related to adverse event	Number of patients with adverse event	Number of patients with prior behavioral abnormalities related to adverse event
Hyperkinesia	7	2	8	4
Hostility	0	0	3	1
Emotional Lability	1	1	8	2
Personality Disorder	0	0	1	0
Suicidal	0	0	1	0

17.2.2 Serious Adverse Events And Adverse Event Discontinuations

17.2.2.1 Serious Behavioral Adverse Events And Behavioral Adverse Event Discontinuations In Study # 86/186

The only serious behavioral adverse event that occurred in this study was an instance of stupor in a patient treated with gabapentin. Behavioral adverse events that led to treatment discontinuation are summarized in the next table; the number of patients with each adverse event is in parentheses

Placebo	Gabapentin
Somnolence and emotional lability (1)	Agitation, hostility, impaired coordination and thinking, reduced pain threshold (1) Increased appetite, insomnia, hostility (1) Personality disorder (1) Insomnia and hyperkinesia (1) Somnolence (1)

3 out of 4 of the above patients appear to have recovered from their behavioral disorder once gabapentin was discontinued. The patient listed as having a

"personality disorder did not: this patient is described as having "appalling behavior" (not further described); an apparent accentuation of a disturbance present at baseline occurred after 2 days of treatment with gabapentin leading to discontinuation of the drug on Day 59; this patient's eventual outcome is not clear.

17.2.2.2 Serious Behavioral Adverse Events And Behavioral Adverse Event Discontinuations In Study # 305/405

None occurred in this study

17.2.2.3 Serious Behavioral Adverse Events And Behavioral Adverse Event Discontinuations In Study # 94

A serious behavioral adverse event occurred in 1 gabapentin-treated patient who was described as demonstrating suicidal ideation and hostility (none occurred in placebo-treated patients). The single gabapentin-treated patient with a serious behavioral adverse event had a pre-study history of aggressive behavior and hyperactivity, demonstrated explosive aggressive behavior after treatment with gabapentin 34.4 mg/kg for 85 days, had his treatment interrupted for 12 days, improved by Day 87 and was able to remain in the study despite resumption of gabapentin in the same dose which was continued for another 6 months

Behavioral adverse events leading to treatment discontinuation occurred in 4 gabapentin-treated patients, but in no patient treated with placebo. These adverse events are listed below. 2 patients recovered from these adverse events after treatment discontinuation, in one patient the outcome was unknown, and in the remaining patient recovery had not yet occurred.

- Emotional lability (2 patients)
- Hyperkinesia (1 patient)
- Hyperkinesia, behavioral abnormality and thinking abnormal (1 patient)

17.3 Tabular Summary Of Serious Behavioral Adverse Events And Behavioral Adverse Events Leading To Treatment Discontinuation In Safety Update (Including Integrated Summary of Safety)

The tables below cover gabapentin-treated patients only and are for a total safety database of 696 patients. In preparing the tables I have used the sponsor's line listings and narratives, supplemented by Case Report Forms when needed.

The studies included are the pediatric submission studies: 945-86/186, -87/187, -305/405, -301/401, -94 and -95

17.3.1 Serious Behavioral Adverse Events

These events are summarized in the following table

Study #	Center/ Patient #	Age/ Gender	Duration of Treatment At Onset (Days)	Dose of Gabapentin At Onset Mg/Kg/Day	Behavioral And Related Adverse Events	Pre-existing Behavioral Problems	Action	Course
87	21/2	7/M	10	32.3	Confusion, somnolence, urinary incontinence, ataxia*	None	Gabapentin discontinued*	Recovered
187	7/4	10/M	207	20.6	Confusion	Mental retardation	None	Recovered
187	9/3	12/M	121	54.1	Somnolence**	None	Gabapentin dose reduced	Recovered
187	29/7	12/M	49	31.9	Hostility	Mental retardation	Gabapentin discontinued	Recovered
94	11/2	10/M	84	34.4	Hostility (explosive aggressiveness) Suicidal ideation	Aggressiveness and hyperactivity	Gabapentin interrupted***	Recovered
95	12/1	13/M	409	36.6	Emotional lability	Attention deficit disorder with hyperactivity	None	Recovered
301	19/19501	3 months/M	30	30.8	Somnolence****	None	None	Recovered

*Patient had non-convulsive status epilepticus and required intensive treatment with several anticonvulsants after gabapentin was discontinued

**Patient had complex partial status epilepticus causing somnolence which resolved after dose of carbamazepine was increased and dose of gabapentin was reduced

***Gabapentin treatment was interrupted for 12 days; within 2 days the patient had recovered. When gabapentin was resumed in the same dose, the patient was able to take the drug for another 6 months without a recurrence of similarly severe symptoms

****Patient had recurrent somnolence associated with 2 episodes of aspiration pneumonia; gabapentin and other anti-epileptic drugs were withdrawn during each episode

17.3.2 Behavioral Adverse Events Leading To Treatment Withdrawal

These are summarized in the following table

Study #	Center/ Patient #	Age/ Gender	Duration of Treatment At Onset (Days)	Dose of Gabapentin At Onset Mg/Kg/Day	Behavioral And Related Adverse Events	Pre-existing Behavioral Problems	Action	Course
87	21/2	7/M	10	32.3	Confusion, somnolence, urinary incontinence, ataxia*	None	Gabapentin discontinued*	Recovered
86	12/6	9/F	2	18.0	Somnolence, atypical absence and myoclonic seizures	None	Gabapentin discontinued	Somnolence recovered
86	16/7	5/F	2	20.0	Agitation, hostility, abnormal thinking, reduced pain threshold, abnormal coordination	None	Gabapentin discontinued	Recovered
86	17/11	9/M	10	15.9	Insomnia, hostility	Learning difficulties	Gabapentin discontinued	Recovered
86	17/12	7/F	2	15.5	Personality disorder	Behavioral problems	Gabapentin discontinued	Unknown
86	20/1	11/M	20	10.3	Somnolence	None	Gabapentin discontinued	Recovered
87	3/1	9/M	7	28.2	Emotional lability	None	Gabapentin discontinued	Recovered
87	6/1	12/M	0	0**	Hostility, abnormal thinking and sensation of having an aura all the time	None	Gabapentin discontinued	Recovered
87	6/2	11/M	95	28.0	Hyperkinesia, anxiety, apathy, ataxia, tremor, convulsions, speech disorder, urinary incontinence	None	Gabapentin discontinued	Partly recovered
87	6/6	6/F	63	30.0	Personality disorder, aggressive behavior	None	Gabapentin discontinued	Partly recovered
87	21/2	7/M	10	32.3	Ataxia, confusion, somnolence, stupor, urinary incontinence***	None	Gabapentin discontinued	Recovered
87	27/2	9/F	8	33.3	Hostility	"Behavioral problems"	Gabapentin discontinued	Not yet recovered
186	13/2	4/F	10	26.3	Insomnia, hyperkinesia	Psychomotor retardation	Gabapentin discontinued	Recovered
187	1/3	8/F	34	25.0	Hyperkinesia	None	Gabapentin discontinued	Unknown
187	29/7	12/M	57	25.5	Hostility	Mental retardation	Gabapentin discontinued	Recovered
187	33/3	7/M	113	46.4	Confusion	West syndrome	Gabapentin discontinued	Not yet recovered
94	9/11	9/F	8	27.5	Emotional lability	Attention deficit disorder with hyperactivity, temper tantrums	Gabapentin discontinued	Unknown
94	27/1	7/M	29	27.6	Hyperkinesia	None	Gabapentin discontinued	Not yet recovered
94	28/5	6/M	4	28.1	Hyperkinesia, thinking abnormal, emotionally labile	None	Gabapentin discontinued	Recovered
94	48/3	8/M	8	25.9	Emotional lability	None	Gabapentin discontinued	Recovered
95	8/3	9/M	13	36.4	Emotional lability	"Behavioral problems"	Gabapentin discontinued	Recovered
95	24/2	5/M	265	34.0	Emotional lability and	None	Gabapentin	Recovered

					amnesia		discontinued	
95	52/1	4/F	18	56.5	Hostility	None	Gabapentin discontinued	Recovered
301	4/4002	4/M	29	34.3	Hyperkinesia	None	Gabapentin discontinued	Recovered
301	21/21001	3/F	7	37.5	Emotional lability	Down syndrome	Gabapentin discontinued	Recovered
301	28/28003	1/F	3	39.5	Nervousness	Cerebral palsy, developmental delay, irritability	Gabapentin discontinued	Not yet recovered
301	101/ 101504	2/M	2	40.0	Hostility	Developmental speech delay	Gabapentin discontinued	Recovered

*Patient had non-convulsive status epilepticus and required intensive treatment with several anticonvulsants after gabapentin was discontinued

**This patient's behavioral abnormalities seemingly began on the day prior to the first dose of gabapentin being administered. His initial dose of gabapentin was 25.7 mg/kg/day. While receiving gabapentin his dose was first reduced to 17.1 mg/kg/day and eventually to 8.6 mg/kg/day before being discontinued on Day 34.

***At the time these symptoms appeared this patient had an EEG tracing consistent with non-convulsive status epilepticus

17.4 Comments Regarding Behavioral Adverse Events

- Certain caveats may be kept in mind when evaluating the above adverse events
  - The behavioral adverse events listed above are "preferred" terms that have been substituted for investigator terms; as a result the meanings of specific terms may have been altered
  - For practically all the above adverse events, standard definitions and detailed descriptions are lacking; the choice of a specific term to describe an adverse event is likely to have been highly subjective. The terms used to describe specific adverse events also overlap considerably in general usage (e.g., "emotional lability" "personality disorder" and "hostility"). The overall proportion of proportion of unique patients who had one or more components of this group of abnormalities may, thus, be more important than the incidence of individual adverse events.
  - The extent to which such adverse events have been systematically looked for is likely to have varied considerably within and across study centers, and from one study to another. A similar variability probably applies to the identification of pre-existing abnormalities of behavior; in fact, the incidence of prior behavioral abnormalities appears to be rather low for a such a population
  - The studies in this submission are multinational and cross-cultural differences in the extent to which specific adverse events may have been identified may also be expected. In addition a number of centers involved in these studies were in non-English-speaking countries and whether specific terms used by investigators in those countries mean the same as they would when used by an investigator whose first language is English is also unclear
- In the controlled adjunctive therapy studies somnolence does appear to have been more common in gabapentin-treated patients than in those treated with placebo; the converse holds true for the controlled monotherapy study. In controlled adult adjunctive therapy studies, somnolence was again more common with gabapentin than with placebo.
- In either the controlled adjunctive and/or monotherapy studies done in children ≥ 3 years old one or more of the following "non-sedative" adverse events was more common in those treated with gabapentin than in those treated with placebo: emotional lability, hostility, hyperkinesia, insomnia, anxiety, suicidal, personality disorder and psychiatric disorder. Of these the most common were hostility, hyperkinesia and emotional lability. The highest incidence of any once of these adverse events in gabapentin-treated patients

in an individual study was for hostility: 7.6 % in Study # 945-86/186. The overall proportion of gabapentin- and placebo-treated patients affected by one or more of the adverse events in this category in each of the 3 main controlled studies is unclear. One or more components of this group of clinical phenomena were more likely to be responsible for serious adverse events and adverse event discontinuations in those treated with gabapentin as compared with placebo in the same studies. There is no clear evidence that the pre-existing behavioral abnormalities predisposed patients to such adverse events when they were administered gabapentin.

Note that in efficacy studies in adults these adverse events appear to have been no more common in those treated with gabapentin than in those treated with placebo.

- Based on the above table, 3 out of a total of 696 (0.43 %) gabapentin-treated patients belonging to the Pediatric Submission Studies grouping had serious adverse events belonging to the "non-sedative" behavioral category
- Based on the above table, 22 out of a total of 696 (3.2 %) gabapentin-treated patients belonging to the Pediatric Submission Studies grouping discontinued treatment on account of adverse events belonging to the "non-sedative" behavioral category
- Considering the frequency and potential seriousness of such adverse events, a description of them in a separate paragraph of the label appears to be warranted

18. Labeling Review

This has been done separately

19. Financial Disclosure Certification

19.1 Material Submitted

The sponsor considers the following studies to be "covered" under the Financial Disclosure by Clinical Investigators Rule, 21 CFR 54, as revised on 12/31/98.

- Studies ongoing as of 2/2/99: #s 945-305/405 and 945-296
- Studies completed prior to 2/2/98: #s 945-86/186, 945-94 and 945-202

For the remaining investigators in Studies 945-296 and 945-305/405 Form FDA 3454 was submitted, attesting to the absence of the relevant financial interests and arrangements was submitted.

For the studies that were completed prior to 2/2/98, no certification has been submitted.

The sponsor has also listed a number of studies included in this application that are considered "non-covered", based on 21 CFR 54.

19.2 Reviewer's Comments

- The Financial Disclosure Certification submitted by the sponsor is in accordance with 21 CFR 54
- Based on the material submitted, it does not appear readily evident that investigator bias, related to financial interests and arrangements influenced the outcome of the "covered' studies included in this submission.

20. Pediatric Exclusivity

Based on an Agency assessment that the studies reported in the original NDA 21216 application conformed with the contents of the final version of the Written Request, the sponsor was informed on 2/2/00 that pediatric exclusivity for Neurontin® had been granted

21. Comments

21.1 Efficacy

- Using the protocol-designated main primary efficacy analysis (based on the Response Ratio) for Study 945-86/186, gabapentin does appear to be superior to placebo, at a statistically significant level, as an adjunctive treatment for partial seizures in children aged 3 to 12 years.
- There is no clear evidence from Study 945-305/405 or elsewhere that gabapentin has efficacy as an adjunctive treatment for partial seizures in children aged 1 month to 3 years.
- An analysis of the proportion of patients exhibiting a decrease in the ratio of secondarily generalized tonic-clonic seizure rate to partial seizure rate did not reveal a statistically significant superiority of gabapentin to placebo in either study; however the number of patients with secondarily generalized tonic-clonic seizures in Study 945-305/405 was exceedingly small.

21.2 Safety

- The overall spectrum of adverse events in controlled clinical trials in children aged 3 to 12 years, with the exception, possibly, of the behavioral symptoms listed below, was not substantially different from that in adults
- The studies that were carried out in children who ranged in age from 1 month to 3 years were in a cohort that frequently had serious concomitant illnesses The spectrum of such illnesses included, but was not limited to, multiple

congenital anomalies, cerebral palsy, inborn errors of metabolism, phakomatoses, and recurrent pneumonia and other infections. The differences in adverse event spectrum between these patients and older children may be explained as being due to the presence of concomitant illnesses and/or concomitant medications in the former, rather than being due to Neurontin® per se.

- There were no sudden unexplained deaths in the entire pediatric studies cohort (see "Warnings" section of label which describes the experience in a cohort of 2203, mainly adult, patients studied prior to initial marketing of Neurontin®: 8 sudden unexplained deaths were seen in this group but also explains the mortality rate per patient-year of exposure to Neurontin® in this cohort is similar to that in a population of epileptic patients not exposed to Neurontin®).
- There were no adverse events that suggested that gabapentin had serious organ toxicity in this population: the one case each of hepatic failure and leukopenia-thrombocytopenia, reported as serious adverse events, were not plausibly attributable to gabapentin. The incidence of severe neutropenia was similar between the gabapentin and placebo groups in the randomized, placebo-controlled trials.
- Based on a review of narratives and Case Report Forms there appeared to be a fair possibility that the following serious adverse events and/or adverse event discontinuations in this population could be caused by gabapentin
  - Abdominal pain, diarrhea, nausea, vomiting and anorexia
  - Somnolence, confusion and impaired concentration
  - Behavioral disturbances including, but not limited to agitation, emotional lability, hostility, and restlessness
  - Urinary incontinence
  - Fatigue
  - Ataxia and tremor
  - Rash
  - Weight gain
  - Atypical absence and myoclonic seizures

  The frequency of these serious adverse events/adverse event discontinuations was low.
- In the randomized, double-blind, placebo-controlled adjunctive therapy study 945-86/186, the incidence of behavioral adverse events, most commonly hyperkinesia, hostility and emotional lability, was 2- to 3-fold higher in those treated with gabapentin than in those treated with placebo. A roughly similar trend was seen in the randomized, double-blind, placebo-controlled monotherapy study, # 945-94. In contrast, in the previously-reviewed efficacy studies in adults no such trend was seen. This group of adverse events was more commonly serious, and more commonly led to study discontinuation, in those treated with gabapentin than in those treated with placebo. While such adverse events are potentially serious, there is no evidence in this specific submission that patients or others came to serious harm as a result; these adverse events are however worthy of special emphasis in the package insert for this drug

The above data need, however, to be viewed cautiously, and with some skepticism, for the following reasons

- The absolute numbers of patients with behavioral adverse events in either treatment group were small
- It is uncertain (and perhaps doubtful) whether patients were evaluated comprehensively for behavioral abnormalities prior to and during these studies
- There is a lack of uniform criteria for diagnosing such adverse events

- Somnolence was more common in gabapentin-treated patients than in those treated with placebo in the 2 controlled adjunctive therapy studies; the converse was true for the monotherapy study

21.3 Risk-Benefit

The benefits of Neurontin® as an adjunctive treatment for partial seizures in children aged 3 to 12 years appear to outweigh the risks

22. Conclusions

The sponsor has supplied evidence that Neurontin® is both effective and safe as an adjunctive treatment for partial seizures in children aged 3 to 12 years

23. Recommendation

I would recommend that this New Drug Application be approved.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. /S/

rbm 9/28/00
cc:
HFD-120
NDA 21216
Ware

APPEARS THIS WAY
ON ORIGINAL

J. Ware
SEP 11 2000

Review and Evaluation of Clinical Data

NDA	**21216**
Sponsor:	**Parke-Davis**
Drug:	**Gabapentin**
Proposed Indication:	
Material Submitted:	**Original NDA/Draft Labeling**
Correspondence Date:	**12/14/99**
Date Received / Agency:	**12/15/99**
Date Review Completed:	**9/11/00**
Reviewer:	**Ranjit B. Mani, M.D.**

BACKGROUND

This document is a review of the draft labeling contained in an original NDA for the use of gabapentin (Neurontin®) — in the treatment of partial seizures in pediatric patients. Enclosed with the original NDA for gabapentin — were supplemental NDAs for Neurontin® capsules (NDA 20235/S-014) and tablets (NDA-20882/S-002), to which the pediatric safety and efficacy data contained in NDA 21216 is cross-referenced.

The original NDA submission was followed by a 4-Month Safety Update that had a correspondence date of 4/14/00. The Safety Update is being reviewed together with the original NDA submission.

The efficacy and safety data contained in the NDA are reviewed in a separate document.

The following sections of the draft label have been reviewed by me in their entirety or in large measure: Clinical Pharmacology (Clinical Trials subsection only), Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Drug Abuse and Dependence, Overdosage, and Dosage and Administration.

In the draft labeling below

- The text of the proposed labeling for Neurontin®, included in this submission, is in black
- The sponsor's proposed additions to the already-approved labeling for gabapentin are in red
- I have used the red strike-through feature to delete segments of the sponsor's additions when necessary.
- Additions that I have made to the sponsor's labeling are in blue

EDITED DRAFT LABELING

(D)

Number of Pages Redacted 24

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Draft Labeling
(not releasable,