Table 5.39
Incidence of Serious/Life Threatening Treatment Emergent Adverse Experiences on LAMICTAL in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=1091) Patients No.	% [1]	Number of Patients with Maximum Intensity[2] Mild	Moderate	Severe
Total No. of Patients with Serious/Life Threatening Adverse Experiences		113	10.4%	12	49	51
General	REACT AGGRAV	32	2.9%	7	15	10
	REACT UNEVAL	11	1.0%	4	3	3
	INFECT	5	0.5%	0	1	4
	FEVER	3	0.3%	0	2	1
	INJURY ACCID	3	0.3%	0	2	1
	OVERDOSE	2	0.2%	1	1	0
	PAIN	2	0.2%	0	2	0
	PAIN ABDO	2	0.2%	0	2	0
	ABDO ENLARGE	1	0.1%	0	1	0
	ASTHENIA	1	0.1%	0	1	0
	CELLULITIS	1	0.1%	0	0	1
	DEATH	1	0.1%	0	0	1
	EDEMA FACE	1	0.1%	1	0	0
	FLU SYND	1	0.1%	0	0	1
	HEADACHE	1	0.1%	0	1	0
	NEOPL	1	0.1%	0	1	0
	REAC UNEVAL	1	0.1%	0	0	1
	SEPSIS	1	0.1%	0	1	0
	SUICIDE ATTEMPT	1	0.1%	0	0	1
Cardiovascular	CARDIOGENIC SHOCK	1	0.1%	0	0	1
	THROMBOPHLEB DEEP	1	0.1%	0	1	0
Digestive	VOMIT	9	0.8%	1	7	1
	GASTROENTERITIS	4	0.4%	0	4	0
	DIARRHEA	3	0.3%	2	1	0
	ANOREXIA	2	0.2%	0	0	2
	NAUSEA	2	0.2%	0	2	0
	DYSPEPSIA	1	0.1%	0	1	0
	TOOTH DISORDER	1	0.1%	1	0	0
Hemic & Lymphatic	THROMBOCYTOPENIA	3	0.3%	0	1	2
	COAGUL DISORDER	1	0.1%	0	0	1

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=1091) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=595) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=496) as the denominator.

Table 5.39
Incidence of Serious/Life Threatening Treatment Emergent Adverse Experiences on LAMICTAL in All Pediatric Studies

		LAMICTAL Patients (N=1091)				
		Patients		Number of Patients with Maximum Intensity[2]		
Body System	Preferred Adverse Experience Term	No.	%[1]	Mild	Moderate	Severe
Hemic & Lymphatic	PANCYTOPENIA	1	0.1%	0	1	0
Metabolic & Nutritional	DEHYDRAT	3	0.3%	0	3	0
	ACIDOSIS	1	0.1%	0	0	1
	EDEMA	1	0.1%	0	1	0
	HYPOPROTEINEM	1	0.1%	0	1	0
	OBESITY	1	0.1%	0	1	0
	WEIGHT GAIN	1	0.1%	0	0	1
Musculoskeletal	ARTHRALGIA	1	0.1%	0	1	0
	OSTEOMYELITIS	1	0.1%	0	1	0
Nervous System	ATAXIA	3	0.3%	0	2	1
	CONVULS GRAND MAL	3	0.3%	0	1	2
	SOMNOLENCE	3	0.3%	0	1	2
	AGITATION	2	0.2%	1	1	0
	DIZZINESS	2	0.2%	0	2	0
	HYPERTONIA	2	0.2%	0	1	1
	PARALYSIS FACIAL	2	0.2%	1	1	0
	PERSON DISORDER	2	0.2%	0	0	2
	CONVULSIONS	1	0.1%	0	1	0
	COORDINAT ABNORM	1	0.1%	0	0	1
	DYSARTHRIA	1	0.1%	0	0	1
	EDEMA BRAIN	1	0.1%	0	0	1
	EEG ABNORM	1	0.1%	0	0	1
	ENCEPHALITIS	1	0.1%	0	0	1
	GRAND MAL EPILEPTIC CO	1	0.1%	0	0	1
	HOSTILITY	1	0.1%	0	0	1
	HYPERKINESIA	1	0.1%	0	0	1
	INSOMNIA	1	0.1%	0	1	0
	IRRITABILITY	1	0.1%	0	0	1
	NERVOUSNESS	1	0.1%	0	1	0
	NEUROPATHY	1	0.1%	0	1	0
	SLEEP DISORDER	1	0.1%	0	0	1
	SPEECH DISORDER	1	0.1%	0	0	1
	STUPOR	1	0.1%	0	1	0
	THINKING ABNORM	1	0.1%	0	0	1

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=1091) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=595) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=496) as the denominator.

Table 5.39
Incidence of Serious/Life Threatening Treatment Emergent Adverse Experiences on LAMICTAL
in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=1091)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	%[1]	Mild	Moderate	Severe
Respiratory	PNEUMONIA	7	0.6%	0	4	3
	PNEUMONIA ASPIR	3	0.3%	0	3	0
	DYSPNEA	2	0.2%	0	1	1
	LUNG DISORDER	2	0.2%	0	2	0
	BRONCHOSPASM	1	0.1%	0	1	0
	EFFUS PLEURAL	1	0.1%	1	0	0
	PHARYNGITIS	1	0.1%	0	1	0
	RHINITIS	1	0.1%	1	0	0
Skin	RASH	9	0.8%	1	2	6
	ERYTHEMA MULT	1	0.1%	0	1	0
	RASH MAC PAP	1	0.1%	0	0	1
	STEVENS JOHNSON SYND	1	0.1%	0	0	1
	STEVENS-JOHNSON SYNDRO	1	0.1%	0	0	1
Special Senses	EAR DISORDER	2	0.2%	1	1	0
	OTITIS MED	2	0.2%	0	2	0
	KERATITIS	1	0.1%	0	0	1
Urogenital	INFECT URIN TRACT	1	0.1%	0	1	0
Urogenital	MENS DISORDER[4]	1	0.2%	0	0	1
Unknown	CHANGE IN CONVULSION T	1	0.1%	0	1	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=1091) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=595) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=496) as the denominator.

Table 5.44
Incidence of Adverse Experiences Leading to Discontinuation of LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=1091) Patients No.	%	Number of Patients with Maximum Intensity Mild	Moderate	Severe
Discontinued due to AEs Total No. of Patients		103	9.4%	20	48	35
General	REACT AGGRAV	19	1.7%	1	14	4
	FEVER	4	0.4%	1	1	2
	HEADACHE	3	0.3%	1	1	1
	ASTHENIA	2	0.2%	0	2	0
	REACT UNEVAL	2	0.2%	0	2	0
	DEATH	1	0.1%	0	0	1
	EDEMA FACE	1	0.1%	0	0	1
	INFECT	1	0.1%	1	0	0
	PAIN	1	0.1%	0	1	0
	UNEXPECTED BENEFIT	1	0.1%	0	1	0
Cardiovascular	CARDIOGENIC SHOCK	1	0.1%	0	0	1
	HYPERTENS	1	0.1%	0	1	0
	SYNCOPE	1	0.1%	0	1	0
Digestive	VOMIT	4	0.4%	0	3	1
	ANOREXIA	1	0.1%	0	1	0
	CONSTIP	1	0.1%	0	1	0
	LEUKOPLAKIA ORAL	1	0.1%	0	1	0
	LIVER DAMAGE	1	0.1%	1	0	0
	NAUSEA	1	0.1%	0	1	0
Hemic & Lymphatic	COAGUL DISORDER	1	0.1%	0	0	1
	LEUKOPENIA	1	0.1%	0	1	0
	LYMPHADENO	1	0.1%	1	0	0
	PANCYTOPENIA	1	0.1%	0	1	0
	THROMBOCYTOPENIA	1	0.1%	0	1	0
Metabolic & Nutritional	EDEMA	2	0.2%	0	1	1
	ACIDOSIS	1	0.1%	0	0	1
	CREATININE INC	1	0.1%	0	1	0
	DEHYDRAT	1	0.1%	0	1	0
	EDEMA PERIPH	1	0.1%	0	1	0
	WEIGHT LOSS	1	0.1%	0	1	0

Percentage is calculated using the overall number of LAMICTAL Patients (N=1091) as the denominator.
NOTE: Patient 123-2009 discontinued from LAMICTAL therapy with an AE that was not treatment emergent.
Patient 092-5003 discontinued from the study due to increased seizure frequency reported as an AE, but the termination record recorded the reason for discontinuation as 'Other'.

Table 5.44
Incidence of Adverse Experiences Leading to Discontinuation of
LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=1091) Patients No.	%	Number of Patients with Maximum Intensity Mild	Moderate	Severe
Musculoskeletal	CRAMPS LEG	1	0.1%	0	0	1
	SPASM GENERAL	1	0.1%	0	1	0
Nervous System	ATAXIA	6	0.5%	1	3	2
	HOSTILITY	4	0.4%	2	1	1
	SOMNOLENCE	4	0.4%	0	2	2
	AGITATION	3	0.3%	0	1	2
	DYSARTHRIA	2	0.2%	1	0	1
	PERSON DISORDER	2	0.2%	0	2	0
	TREMOR	2	0.2%	1	1	0
	AKATHISIA	1	0.1%	1	0	0
	AMNESIA	1	0.1%	1	0	0
	CONFUS	1	0.1%	0	1	0
	CONVULS GRAND MAL	1	0.1%	0	0	1
	CONVULSIONS	1	0.1%	0	1	0
	COORDINAT ABNORM	1	0.1%	0	0	1
	DIZZINESS	1	0.1%	0	1	0
	EDEMA BRAIN	1	0.1%	0	0	1
	EEG ABNORM	1	0.1%	0	0	1
	EMOTION LABIL	1	0.1%	0	0	1
	ENCEPHALITIS	1	0.1%	0	0	1
	HYPERKINESIA	1	0.1%	0	0	1
	HYPERTONIA	1	0.1%	0	0	1
	INSOMNIA	1	0.1%	1	0	0
	NERVOUSNESS	1	0.1%	1	0	0
	PARESTHESIA	1	0.1%	0	1	0
	SLEEP DISORDER	1	0.1%	0	0	1
	SPEECH DISORDER	1	0.1%	0	1	0
	THINKING ABNORM	1	0.1%	0	0	1
Respiratory	PHARYNGITIS	2	0.2%	2	0	0
	BRONCHITIS	1	0.1%	1	0	0
	DYSPNEA	1	0.1%	0	0	1
	EFFUS PLEURAL	1	0.1%	1	0	0
	EPISTAXIS	1	0.1%	1	0	0
	HYPERVENTIL	1	0.1%	0	1	0
	LUNG DISORDER	1	0.1%	0	1	0
	PNEUMONIA	1	0.1%	0	1	0

Percentage is calculated using the overall number of LAMICTAL Patients (N=1091) as the denominator.
NOTE: Patient 123-2009 discontinued from LAMICTAL therapy with an AE that was not treatment emergent.
Patient 092-5003 discontinued from the study due to increased seizure frequency reported as an AE, but the termination record recorded the reason for discontinuation as 'Other'.

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Table 5.44
Incidence of Adverse Experiences Leading to Discontinuation of LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=1091) Patients No.	Patients % [1]	Number of Patients with Maximum Intensity Mild	Moderate	Severe
Skin	RASH	40	3.7%	10	17	13
	RASH MAC PAP	9	0.8%	3	3	3
	ALOPECIA	1	0.1%	0	0	1
	ECZEMA	1	0.1%	1	0	0
	ERYTHEMA MULT	1	0.1%	0	1	0
	HIRSUTISM	1	0.1%	0	0	1
	STEVENS JOHNSON SYND	1	0.1%	0	0	1
	STEVENS-JOHNSON SYNDRO	1	0.1%	0	0	1
Urogenital	MENS DISORDER	1	0.2%	0	0	1
Unknown	CHANGE IN CONVULSION T	1	0.1%	0	1	0

[1] Percentage is calculated using the overall number of LAMICTAL Patients (N=1091) as the denominator.
NOTE: Patient 123-2009 discontinued from LAMICTAL therapy with an AE that was not treatment emergent.
Patient 092-5003 discontinued from the study due to increased seizure frequency reported as an AE, but the termination record recorded the reason for discontinuation as 'Other'.

Table 5.29

Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies (Except LAMICTAL Study 026)

		LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[1]		
Body System	Preferred Adverse Experience Term	No.	%[1]	Mild	Moderate	Severe
Total No. of Patients with Adverse Experiences		555	79.7%	202	257	96
General	INFECT	120	17.2%	83	30	7
	REACT AGGRAV	81	11.6%	18	47	13
	FEVER	77	11.1%	54	18	4
	HEADACHE	76	10.9%	60	12	4
	INJURY ACCID	43	6.2%	24	15	3
	PAIN ABDO	43	6.2%	33	10	0
	ASTHENIA	40	5.7%	25	15	0
	REACT UNEVAL	37	5.3%	15	17	4
	FLU SYND	25	3.6%	22	3	0
	PAIN	20	2.9%	17	3	0
	ALLERG REACT	6	0.9%	2	3	1
	PAIN CHEST	6	0.9%	6	0	0
	EDEMA FACE	5	0.7%	4	0	1
	PAIN BACK	4	0.6%	3	1	0
	OVERDOSE	3	0.4%	1	2	0
	HALITOSIS	2	0.3%	1	1	0
	MALAISE	2	0.3%	2	0	0
	PAIN NECK	2	0.3%	2	0	0
	UNEXPECTED BENEFIT	2	0.3%	1	1	0
	CELLULITIS	1	0.1%	0	0	1
	CHILLS	1	0.1%	1	0	0
	LAB TEST ABNORM	1	0.1%	1	0	0
	MONILIA	1	0.1%	1	0	0
	NEOPL	1	0.1%	0	1	0
	OVERDOSE ACCID	1	0.1%	0	1	0
	PAIN BREAST	1	0.1%	1	0	0
	PHOTOSENSITIVITY	1	0.1%	1	0	0
	SEPSIS	1	0.1%	0	1	0
	SUICIDE ATTEMPT	1	0.1%	0	0	1
Cardiovascular	HEMORR	4	0.6%	4	0	0
	PALLOR	3	0.4%	1	2	0
	ANGINA PECTORIS	2	0.3%	2	0	0
	SYNCOPE	2	0.3%	1	1	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [2] and [3].

[2] Intensity Classification was occasionally missing.

[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.

[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies
(Except LAMICTAL Study 026)

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	%[1]	Mild	Moderate	Severe
Cardiovascular	PALPITAT	1	0.1%	1	0	0
	VASC DISORDER PERIPH	1	0.1%	1	0	0
	VASODILAT	1	0.1%	1	0	0
Digestive	VOMIT	99	14.2%	58	39	2
	NAUSEA	40	5.7%	37	3	0
	DIARRHEA	34	4.9%	26	8	0
	ANOREXIA	21	3.0%	13	6	2
	CONSTIP	16	2.3%	10	5	1
	SALIVA INC	15	2.2%	8	6	1
	GASTROENTERITIS	13	1.9%	7	6	0
	DYSPEPSIA	8	1.1%	6	2	0
	TOOTH DISORDER	6	0.9%	4	1	1
	APPETITE INC	4	0.6%	2	2	0
	DYSPHAGIA	3	0.4%	0	2	1
	GINGIVITIS	3	0.4%	3	0	0
	ULCER MOUTH	3	0.4%	2	0	0
	FLATUL	2	0.3%	1	1	0
	GASTRITIS	2	0.3%	2	0	0
	GASTROINTESTINAL DISOR	2	0.3%	1	1	0
	STOMATITIS APHTH	2	0.3%	1	1	0
	CANDIDIASIS OF MOUTH	1	0.1%	1	0	0
	GINGIVAL HEMORRHAGE	1	0.1%	1	0	0
	MELENA	1	0.1%	1	0	0
	MONILIA ORAL	1	0.1%	1	0	0
	RECTAL HEMORRHAGE	1	0.1%	1	0	0
	STOMATITIS	1	0.1%	1	0	0
	STOOL ABNORM	1	0.1%	1	0	0
	THIRST	1	0.1%	1	0	0
Endocrine	HYPOTHYR	2	0.3%	2	0	0
	CUSHINGS SYND	1	0.1%	0	1	0
Hemic & Lymphatic	ANEMIA	7	1.0%	4	2	1
	LYMPHADENO	4	0.6%	3	1	0
	LYMPHADENOPATHY	4	0.6%	2	2	0
	LEUKOPENIA	3	0.4%	2	1	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

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Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies
(Except LAMICTAL Study 026)

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	%[1]	Mild	Moderate	Severe
Hemic & Lymphatic	ANEMIA IRON DEFIC	1	0.1%	1	0	0
	EOSINOPHILIA	1	0.1%	1	0	0
	LEUKOCYTOSIS	1	0.1%	1	0	0
	PLAT ABNORM	1	0.1%	1	0	0
	THROMBOCYTOPENIA	1	0.1%	0	0	1
Metabolic & Nutritional	WEIGHT INC	6	0.9%	4	1	1
	EDEMA	5	0.7%	3	1	1
	WEIGHT DEC	4	0.6%	1	3	0
	WEIGHT LOSS	4	0.6%	1	3	0
	EDEMA PERIPH	2	0.3%	1	1	0
	OBESITY	2	0.3%	0	2	0
	WEIGHT GAIN	2	0.3%	2	0	0
	ANEMIA IRON DEFIC	1	0.1%	1	0	0
	CREATININE INC	1	0.1%	0	0	1
	HYPERGLYCEMIA	1	0.1%	1	0	0
	SGOT INC	1	0.1%	0	1	0
	SGPT INC	1	0.1%	1	0	0
Musculoskeletal	MYALGIA	6	0.9%	5	1	0
	MYASTHENIA	4	0.6%	3	1	0
	TWITCH	2	0.3%	0	1	1
	ARTHRALGIA	1	0.1%	1	0	0
	ARTHRITIS	1	0.1%	1	0	0
	OSTEOMYELITIS	1	0.1%	0	1	0
	SPASM GENERAL	1	0.1%	0	1	0
Nervous System	SOMNOLENCE	94	13.5%	52	37	5
	DIZZINESS	46	6.6%	37	8	1
	ATAXIA	44	6.3%	18	19	7
	TREMOR	36	5.2%	24	11	1
	INSOMNIA	26	3.7%	15	10	1
	NERVOUSNESS	24	3.4%	16	8	0
	HYPERKINESIA	20	2.9%	5	14	1
	THINKING ABNORM	20	2.9%	11	7	2
	PERSON DISORDER	18	2.6%	7	10	1
	HOSTILITY	17	2.4%	9	6	2

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

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Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies
(Except LAMICTAL Study 026)

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N= 696) Patients No.	% [1]	Number of Patients with Maximum Intensity [2] Mild	Moderate	Severe
Nervous System	EMOTION LABIL	15	2.2%	7	6	2
	AGITATION	10	1.4%	5	3	2
	GAIT ABNORM	10	1.4%	6	2	2
	HYPERACTIVITY	10	1.4%	8	1	1
	IRRITABILITY	9	1.3%	7	1	1
	DREAM ABNORM	7	1.0%	3	3	1
	DYSARTHRIA	6	0.9%	4	1	1
	HYPERTONIA	6	0.9%	1	4	1
	SLEEP DISORDER	6	0.9%	4	1	1
	VERTIGO	6	0.9%	5	1	0
	AKATHISIA	5	0.7%	2	1	2
	CNS DEPRESS	5	0.7%	5	0	0
	DEPRESSION	5	0.7%	2	2	1
	AMNESIA	4	0.6%	2	2	0
	CONFUS	4	0.6%	1	3	0
	CONVULSIONS	4	0.6%	3	1	0
	COORDINAT ABNORM	4	0.6%	2	1	1
	NYSTAGMUS	4	0.6%	3	1	0
	SPEECH DISORDER	4	0.6%	1	2	1
	CONFUSION	3	0.4%	3	0	0
	CONVULS	3	0.4%	2	1	0
	HYPOTONIA	3	0.4%	1	1	1
	ANXIETY	2	0.3%	1	1	0
	APHASIA	2	0.3%	1	1	0
	CNS STIMULAT	2	0.3%	2	0	0
	CONVULS GRAND MAL	2	0.3%	0	2	0
	COVULS GRAND MAL	2	0.3%	0	1	1
	HALLUCIN	2	0.3%	1	1	0
	HALLUCINATIONS	2	0.3%	0	2	0
	HYPOESTHESIA	2	0.3%	2	0	0
	MYOCLONUS	2	0.3%	1	1	0
	PANIC ATTACK	2	0.3%	2	0	0
	PARALYSIS FACIAL	2	0.3%	1	1	0
	APATHY	1	0.1%	0	1	0
	CEREBELL SYND	1	0.1%	1	0	0
	CHOREOATHETOSIS	1	0.1%	1	0	0
	DYSKINESIA	1	0.1%	1	0	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies
(Except LAMICTAL Study 026)

		LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[2]		
Body System	Preferred Adverse Experience Term	No.	%[1]	Mild	Moderate	Severe
Nervous System	DYSTONIA	1	0.1%	0	1	0
	EDEMA BRAIN	1	0.1%	0	0	1
	EEG ABNORM	1	0.1%	0	0	1
	GRAND MAL EPILEPTIC CO	1	0.1%	0	0	1
	HYPERSALIVATION	1	0.1%	1	0	0
	MENTAL RETARD	1	0.1%	1	0	0
	MOTOR DYSFUNCTION	1	0.1%	0	1	0
	NEUROSIS	1	0.1%	0	1	0
	PARESTHESIA	1	0.1%	0	1	0
	STUPOR	1	0.1%	0	1	0
	VASODILAT	1	0.1%	1	0	0
Respiratory	PHARYNGITIS	76	10.9%	55	19	1
	RHINITIS	59	8.5%	52	7	0
	COUGH INC	30	4.3%	28	2	0
	BRONCHITIS	27	3.9%	17	9	1
	RESPIRAT DISORDER	25	3.6%	13	11	0
	EPISTAXIS	11	1.6%	9	2	0
	LUNG DISORDER	9	1.3%	5	3	1
	PNEUMONIA	7	1.0%	1	5	1
	SINUSITIS	7	1.0%	5	2	0
	BRONCHOSPASM	6	0.9%	3	3	0
	DYSPNEA	4	0.6%	3	1	0
	APNEA	1	0.1%	0	1	0
	HYPERVENTIL	1	0.1%	0	1	0
	LARYNGITIS	1	0.1%	1	0	0
	PNEUMONIA ASPIR	1	0.1%	0	1	0
Skin	RASH	94	13.5%	56	24	14
	RASH MAC PAP	15	2.2%	10	3	2
	ECZEMA	12	1.7%	10	2	0
	ALOPECIA	7	1.0%	5	1	1
	HERPES ZOSTER	6	0.9%	3	3	0
	PRURITUS	6	0.9%	4	2	0
	RASH VESIC BULL	6	0.9%	6	0	0
	ACNE	3	0.4%	2	1	0
	DERM CONTACT	3	0.4%	3	0	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

Table 5.29

Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies (Except LAMICTAL Study 026)

		LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[3]		
Body System	Preferred Adverse Experience Term	No.	%[1]	Mild	Moderate	Severe
Skin	FURUNCULOSIS	3	0.4%	2	1	0
	HERPES SIMPLEX	3	0.4%	2	0	1
	NAIL DISORDER	3	0.4%	3	0	0
	SKIN DISORDER	3	0.4%	2	1	0
	EXFOLIATIVE DERMATITIS	2	0.3%	2	0	0
	HIRSUTISM	2	0.3%	0	0	2
	SKIN DRY	2	0.3%	2	0	0
	URTICARIA	2	0.3%	1	1	0
	DERM FUNG	1	0.1%	1	0	0
	DRYNESS OF SKIN	1	0.1%	1	0	0
	ERYTHEMA MULT	1	0.1%	0	1	0
	HAIR DISORDER	1	0.1%	1	0	0
	NEOPL SKIN	1	0.1%	1	0	0
	NEOPLASM OF SKIN	1	0.1%	1	0	0
	PUSTULAR RASH	1	0.1%	1	0	0
	SKIN ULCER	1	0.1%	1	0	0
	STEVENS JOHNSON SYND	1	0.1%	0	0	1
	STEVENS-JOHNSON SYNDRO	1	0.1%	0	0	1
	SWEAT	1	0.1%	1	0	0
	SWEATING	1	0.1%	1	0	0
Special Senses	OTITIS MED	32	4.6%	21	11	0
	DIPLOPIA	19	2.7%	11	5	3
	EAR DISORDER	10	1.4%	8	2	0
	BLURRED VISION	9	1.3%	5	4	0
	PAIN EAR	9	1.3%	8	1	0
	CONJUNCTIVITIS	7	1.0%	6	1	0
	AMBLYOPIA	5	0.7%	4	1	0
	VISION ABNORM	4	0.6%	3	1	0
	VISUAL IMPAIRMENT	3	0.4%	3	0	0
	PAIN EYE	2	0.3%	2	0	0
	STRABISMUS	2	0.3%	2	0	0
	BLEPHARITIS	1	0.1%	0	1	0
	DRY EYE(S)	1	0.1%	1	0	0
	EYE DISORDER	1	0.1%	0	1	0
	KERATITIS	1	0.1%	0	0	1
	OTITIS EXT	1	0.1%	0	1	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [2] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences on LAMICTAL Treatment in All Pediatric Studies
(Except LAMICTAL Study 026)

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N= 696)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	%[1]	Mild	Moderate	Severe
Special Senses	OTITIS EXTERNA	1	0.1%	1	0	0
	PHOTOPHOBIA	1	0.1%	0	1	0
	TASTE PERVERS	1	0.1%	1	0	0
Urogenital	INFECT URIN TRACT	11	1.6%	5	6	0
	INCONTIN URIN	4	0.6%	2	2	0
	URINE INCONTINENCE	3	0.4%	3	0	0
	HEMATURIA	2	0.3%	2	0	0
	PYELONEPHRITIS	2	0.3%	2	0	0
	URIN FREQUENCY	2	0.3%	1	1	0
	URIN RETENT	2	0.3%	1	1	0
	ALBUMINURIA	1	0.1%	0	1	0
	CYSTITIS	1	0.1%	1	0	0
	DYSURIA	1	0.1%	1	0	0
	POLYURIA	1	0.1%	1	0	0
	SEX MAT ACCEL	1	0.1%	1	0	0
	URIN IMPAIRED	1	0.1%	0	1	0
Urogenital	DYSMENORRHEA[4]	2	0.6%	1	1	0
	VAGINITIS[4]	1	0.3%	1	0	0
Urogenital	PENIS DISORDER[3]	2	0.5%	2	0	0
	BALANITIS	1	0.1%	1	0	0
Unknown	CHANGE IN CONVULSION T	1	0.1%	0	1	0

APPEARS THIS WAY
ON ORIGINAL

[1] Percentage is calculated using the overall number of LAMICTAL patients (N= 696) as the denominator. Exceptions are the gender specific AEs. See [3] and [4].
[2] Intensity Classification was occasionally missing.
[3] Percentage is calculated using the overall number of male LAMICTAL patients (N=382) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=314) as the denominator.

Review and Evaluation of Clinical Data
NDA 20-764

Sponsor:	Burroughs Wellcome Co.
Drug:	Lamictal (lamotrigine) Chewable Dispersible
Proposed Indication:	Lenox-Gastaut Syndrome
Material Submitted:	Response to FDA Request (5 volumes) and Proposed Briefing Document
Correspondence Date:	July 22, 1997 and October 21, 1997, respectively

My original safety review of this NDA, dated March 7, 1997, discussed the dermatologic adverse events reported in the sponsor's NDA submission. The conclusions reached in that review were based on a pediatric NDA safety database comprising 399 individuals, limited information about prevalence of proposed risk factors in that population, and limited information about the rashes seen. The upper limit for the risk of SJS was placed at about 1 in 50 which was at least the incidence of SJS in Study 123, the randomized trial in Lenox-Gastaut Syndrome.

The sponsor was made aware of our concerns during discussions that resulted in the incorporation of a Black Box Warning in the approved labeling for Lamictal.

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1. In response to our concerns, the sponsor obtained two outside consultants to review all cases of hospitalized rashes in the pediatric development project. The differing views of the two consultants on the formal classification of rashes demonstrates the uncertainty that arises using formal case classification to determine rates. The uncertainty was further demonstrated when our own internal dermatologic consultant attempted to formally classify cases, with results that differed from both of the sponsor's consultants.

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Because of this, discussions about this NDA moved from a discussion of SJS to a discussion of hospitalized rash. Because of the remote chance that a case of SJS could be managed as an out-patient, discussions with the sponsor centered on **"serious rash"** defined as a rash called SJS/TEN by the primary investigator or hospitalized. In the database, there was a

single case of a rash called SJS by the primary investigator, but never hospitalized.

2. The second important development after my March 7th review was the expansion of the pediatric NDA database. On page 25 of my March 7th review, I commented on Compassionate Use Protocol 26 in the U.S. That protocol included several hundred children, but at that time, the sponsor did not feel it appropriate to merge U.S. 26 with the rest of the database because the 26 database had not been locked and quality assured.

During the NDA review time, safety data from several studies was quality assured, so that the final denominator for safety included the 399 patients in the NDA, plus new exposures from studies 40 (n=98), 44 (n=45), 126, 136, 41, and 26. The poolability of the studies was deemed appropriate given the uniform reporting rates for "serious rash" (defined above) across the original 399 and the additional 700 patient cohort. (In a July 29, 1997 amendment, the sponsor responded to our concerns by describing the procedures for quality assuring the Protocol 26 safety database.) The final denominator agreed upon was 1071 pediatric subjects.

3. In the July 22, 1997 submission, the sponsor provided detailed information about concomitant VPA usage and dose escalation regimens (the 2 previously identified risk factors for rash with Lamictal) for the 1071 individuals.

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ON ORIGINAL

While the July 22 submission was under review, DNDP made plans to bring the NDA to the Peripheral and Central Nervous System Advisory Committee for discussion of the dermatologic risk of the drug in children. However, as the review process continued (spurred along in large part by efforts to create a joint briefing document for the advisory committee from the sponsor and the division), it became clear that reasonable risk estimates were not as high as originally thought and there was no rash-related mortality or disability described in the NDA database. Given the severe nature of the Lenox-Gastaut Syndrome and the dearth of satisfactory treatments, the review team unanimously agreed that an approval action could be reasonably made without the input of the advisory committee.

New Denominator for Risk Calculation: There are 2 working denominators in the July 22nd submission: the sponsor's primary database (n=542) and secondary database (n=1111).

The primary database includes the 399 patients in the NDA, plus new exposures from studies 40 (n=98) and 44 (n=45).

The secondary database includes the primary database plus new exposures from studies 126, 136, 41, and 26.

However, by the October 21st document, the division and the sponsor had agreed that this dichotomy, primary vs. secondary databases, was distracting and it was appropriate to refer only to the aggregate, n=1111. The poolability of the data was addressed above and was judged valid, given the uniform rates of "serious rash" across the two different subgroupings of studies.

Page 20 of the October 21st document addresses the denominator used in further rate calculations. Of the 1111 patients in the Glaxo "pediatric" clinical trials database, 41 were 16 years of age or older. Therefore, 1070 represents the number < 16 years of age in the database. An additional patient in Study 26 that developed a rash after the time of data cutoff was added. Therefore, 1071 represents the denominator used in further rate calculations.

There is also a small cohort of Japanese pediatric patients, n=162, exposed to Lamictal in Japanese studies. The Japanese data has not been quality assured (studies are still ongoing), however, and the 162 cases are not pooled with the 1071.

Cohort of 18 Patients with Serious Rash: In Section C of the July 22nd submission, the sponsor reports that a total of 18 cases of "serious rash" have been identified among all Lamictal treated pediatric patients enrolled in clinical trials. These 18 are listed in Sponsor's Table B12. It is somewhat confusing that all 18 cases are discussed, because 3/18 exist in the Japanese experience and are, therefore, not used in further rate calculations.

The following 2 cases (non-Japanese) are excluded from further discussion by the sponsor, leaving a cohort of 16.

o Pt 26-38-7 was hospitalized for seizures and rash but discharged from the hospital still taking Lamictal

o Pt 26-54-10 is indicated in the database as being hospitalized, but the clinical report shows the patient was not hospitalized

No narratives or CRFs were initially provided for these 2 patients and the dermatology consultant did not review any data on these 2 patients. Descriptions of the 2 provided in the October 21st submission (p21) reveal that the first was hospitalized primarily for seizure control and the rash was mild; the second case was a moderate rash only.

The July 22nd submission states that narratives are included for the 16 patients, but really only 13 narratives are provided. The excluded narratives are for Pts 26-2-1 (pathologic diagnosis of Hanta virus); Japan B41225; and Japan B40594. The Hanta virus case has been well-described previously, while the other 2 narratives were provided in an August 28, 1997 submission at my request.

CRFs are provided for 14 patients. Excluded CRFs among the cohort of 16 include Pts 126-132-4021 and 136-28813043; these CRFs were added in the August 28, 1997 submission.

Classification of 16 Patients: 7/16 are only in secondary database; 6/16 are in primary and thus, also, in secondary database (4 of these 6 were in the original NDA, while 2 of these 6 are new additions). 3/16 are in Japanese studies.

However, the sponsor excludes 2 more patients from their analyses below for the following reasons:

o Pt 26-2-1 had a fatal illness with rash as one component; at autopsy, hantavirus was confirmed. Two weeks after starting Lamictal this child had a diffuse macular rash, shallow ulcers in her mouth, and conjunctivitis. The cause of death was pulmonary failure with ARDS.

o Pt 26-9-1 was hospitalized with a reaction attributed to phenobarb. There is no mention of mucosal involvement or skin blistering. Lamictal was continued for another 5 months.

Another case was excluded from analyses of "serious rash" in the first submission, but re-introduced into the analyses for the Oct submission after reconsideration by the sponsor:

o Pt 26-6-05 had been on Lamictal for 200 days and then had phenytoin added to the regimen; 6 weeks later a rash developed which resolved after Lamictal was stopped and phenytoin continued. The sponsor contended earlier that this rash was due to phenytoin. Nothing in the AE report suggests the presence of mucosal involvement or blistering of the skin. The main reason for hospitalization was control of increased seizures.

Therefore, a total of 11 patients are included in the sponsor's analyses of "serious rash" in the Oct briefing document. The rate of "serious rash" is therefore 11/1071.

Original Classification of these 11 Cases by the Primary Investigators: Based on the original diagnosis entered in the company safety database, there are 5 cases of possible SJS.

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ON ORIGINAL

Based on these 5 cases, the rate of possible SJS would be 5/1071.

Risk Factors: For "serious rash," there really is no difference in risk whether dosed "correctly" (4/294) or "incorrectly" (7/740), using current European dosing guidelines. Note that dosing information was only available for 1034/1071 patients. All 5 cases of possible SJS were dosed incorrectly.

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ON ORIGINAL

For "serious rash," there really is no difference in risk whether dosed with concurrent VPA (5/443) or not (6/628). The risk of possible SJS is 4-5-fold greater in patients dosed with concurrent VPA (4/443) vs those not on concurrent VPA (1/628).

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ON ORIGINAL

Sponsor's Consultants' Classification of these 11 Cases: The sponsor had 2 dermatology consultants, working independently, classify cases. Dr. Neil Shear classified only 1/11 as SJS. Additionally, he classified 2 of the Japanese cases as SJS possibly due to Lamictal.

Based on his cases, the rate of SJS possibly due to Lamictal would be 1/1071 (ignoring the Japanese experience).

Of the 11 cases, Dr. Robert Stern has classified 4 as SJS. Additionally, he classified 1 of the Japanese cases as SJS.

Based on his cases, the rate of SJS would be 4/1071 (ignoring the Japanese experience).

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ON ORIGINAL

FDA's Dermatologic Consultant's Classification of the 11 Cases: In a review dated October 8, 1997 (faxed to DNDP on October 21), Dr. Ella Toombs, a reviewer in the Division of Dermatologic and Dental Drug Products, reported that none of the cases could be definitely diagnosed as SJS based on the information given.

Conclusions: Since the submission of NDA 20-764, the sponsor has compiled more data about the patients who experienced rashes in the NDA database. Even with this new data, however, several dermatologic experts disagreed about the final classification of the rashes seen in the NDA, specifically about applying the label "SJS" to given cases. It was this disagreement which gave rise to a broader discussion of "serious rash" within the NDA experience.

"Serious rash," too, is an imperfect classification. The vast majority (all but one) of the cases falling into this classification did so simply because there was a hospitalization, with the main reason for hospitalization being rash. There *is* some arbitrariness involved in the decision whether or not to hospitalize a patient. But from our current position, looking back in time, there can be no post hoc changing of the fact that a patient was or was not hospitalized. Further, the decision to hospitalize was distributed among many primary investigators and cannot be usurped by a single expert. For these reasons, "serious rash" is informative.

For the same reasons, the primary investigators' original classification of cases as SJS is perhaps as valuable as a single expert's retrospective view of the situation. In this regard, there were 4 cases called SJS in the original safety database of 399 submitted with the NDA, for a risk of 1/100. In the expanded NDA database, only 1 additional case was called SJS, for a risk of 5/1071 or 1/200.

A risk of 1/200 is still high, but is not as alarming as 1/100 or 1/50. (Note that 1/50 was the risk seen in several independent, smaller series, including the Lenox-Gastaut study, the Dooley article, and the Arnold abstract.) More reassuring, still, is that there were no rash-related deaths in the cohort of 1071; nor are sequelae with disability described.

Lenox-Gastaut Syndrome is a horrible disorder. Because of the refractory nature of the seizures in the syndrome, greater risk will undoubtedly be acceptable to the community in the hope of seeking better seizure control.

Plan: The safety data supports an approvable action for the use of Lamictal in the Lenox-Gastaut Syndrome. Given the new expanded database, the risk estimate for "serious rash" in those under the age of 16 years is 1/100. There is no evidence from the expanded database that concomitant VPA impacts the risk of "serious rash," but there is a signal that those hospitalized rashes which are more likely to be classified as SJS are also more likely to be associated with concomitant VPA use. These points should be made in labeling.

/S/

APPEARS THIS WAY
ON ORIGINAL

John Feeney, M.D.
Medical Reviewer
November 13, 1997

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-120
NDA 20-764
HFD-120/Leber/Katz/Feeney/Ware

Div. File

MAR 7 1997

CLINICAL SAFETY REVIEW

NDA 20-764

LAMICTAL CD (lamotrigine)

Indication 1: Adjunctive Treatment of Lennox-Gastaut Syndrome

Reviewer:	John Feeney, M.D.
Date:	March 7, 1997
Sponsor:	Glaxo Wellcome
Indication:	Epilepsy
NDA Submission Date:	September 16, 1996

Table of Contents

Volumes 47-50 of the submission contain the Integrated Summary of Safety for the indication "Treatment of Lennox-Gastaut Syndrome," and are the primary source of information for this review.

Also incorporated into this review were the safety update submitted January 17, 1997 and the sponsor's submission of February 4, 1997 containing the sponsor's risk reduction strategy for rash.

1.0 Exposure

In order to develop a safety profile of Lamictal in a pediatric population, the sponsor merged safety data from 6 pediatric studies (UK 61,73,92,98,102,and 123) and one long-term continuation study (UK 114). UK 123 was conducted in patients with Lennox-Gastaut Syndrome, while the other studies included children with treatment-resistant epilepsy. This "NDA database" comprises 399 unique pediatric patients: 320 patients in open-label trials and 79 patients in the controlled trial, UK 123. There were 90 placebo patients in UK 123.

Additional sources of data include:

1. studies conducted by local operating companies,
2. ongoing clinical trials in pediatric patients,
3. US compassionate plea trial, US 26,
4. European "named" (compassionate use) patients, and
5. spontaneous post-marketing reports through December 31, 1995.

A list of pediatric trials is attached.

In the NDA database, almost all patients were on concomitant AEDs as follows:

EIAEDs alone	37%
VPA + EIAEDs	19%
VPA + non-EIAEDs	33%
Lamictal monotherapy	2%
Other concomitant AEDs	9%

244 pts were exposed for at least 6 months to Lamictal. 188 pts were exposed for at least 1 year.

Table of All Studies
Summary of Key Characteristics of Clinical Studies Included in Indication 1 – Treatment of Lennox–Gastaut Syndrome

Protocol Number	Study[a]		Control[b] (daily dose mg/day)	LAMICTAL Treatment			Completion Status	No. Entered	Age Range (yrs)	Number Exposed to LTG	Patient Type
	Objective	Design		Regimen/ formulation[c]	Duration (weeks)	Doses (mg/day)					
Clinical Pharmacology Studies											
US 47	PK	OL C	None	single dose CD	2 days	100	Completed	6		6	Normal Adult Volunteers
UK 120	PK	OL C	None	single dose cap, CD	2 days	25	Completed	12		12	Normal Adult Volunteers
UK 121	PK	OL C	None	single dose cap, CD	2 days	100	Completed	12		12	Normal Adult Volunteers
UK 134	PK	OL C	None	single dose cap, CD	2 days	100	Completed	12		12	Normal Adult Volunteers
US 39	PK	OL C	None	single dose tab, CD	2 days	25	Completed	18		18	Normal Adult Volunteers
US 48	PK	OL C	None	single dose tab, CD	2 days	100	Completed	17		17	Normal Adult Volunteers
US 49	PK	OL C	None	single dose tab, CD	2 days	25	Completed	18		18	Normal Adult Volunteers
US 50	PK	OL C	None	single dose tab, CD	2 days	25	Completed	17		17	Normal Adult Volunteers
US 51	PK	OL C	None	single dose tab, CD	2 days	100	Completed	18		28	Normal Adult Volunteers

[a] S = Safety, DB–P = Double–Blind Parallel, OL = Open–Label, LTC = Long–Term Continuation, C = Crossover, RE = Responder Enriched.
[b] PBO = placebo
[c] b.i.d. = twice a day, q.d. = once a day, cap = capsule, C–D = chewable/dispersible, tab = compressed tablet.
[d] VPA = sodium valproate.
[e] UK 611 is the long term continuation of UK 61.
[f] UK 114 is the long term continuation of UK 73, UK 98, and UK 102. The long–term continuation patients for UK 92 are included although they were continued in the primary study by an amendment instead of entering study UK 114.
[g] US 41 is the long term continuation of US 40, US 44, and for US patients in UK 123.

Table of All Studies
Summary of Key Characteristics of Clinical Studies Included in Indication 1 – Treatment of Lennox–Gastaut Syndrome (continued)

Protocol Number	Study[a]		Control[b] (daily dose mg/day)	LAMICTAL Treatment			Completion Status	No. Entered	Age Range (yrs)	Number Exposed to LTG	Patient Type
	Objec-tive	Design		Regimen/ formulation[c]	Duration (weeks)	Doses (mg/day)					
Controlled Study											
UK 123 53 centers 14 countries	S, E	DB–P	PBO	q.d./b.i.d UK, CD	4 (single blind PBO) 8 (escalation) 8 (maintenance) Total 20	0 at baseline Maintenance based on wt and VPAd use 1–5mg/kg with VPA; 10–15 mg/kg without VPA	Completed 1 Nov 95	179 (169 rand.)		79	Lennox–Gastaut syndrome
Uncontrolled Study											
UK 61(1)[e]	PK	OL	None	q.d./b.i.d cap	4 (escalation) 44 (maintenance) 4 (taper off) Total 52	12.5–600	Completed	20		20	Treatment Resistant
UK 73	Dosing	OL	None	q.d./b.i.d. cap	8 (escalation) 40 (maintenance) 4 (taper off) Total 52	25–500	Completed	61		59	Treatment Resistant
UK 92	Dosing	OL	None	b.i.d. cap, CD	4 (placebo) 8 (escalation) 40 (maintenance) 4 (taper off) Total 56	6.25–400	Completed	29		29	Treatment Resistant
UK 98	S	OL	None	b.i.d. cap	4 (escalation) 44 (maintenance) 4 (taper off) Total 52	12.5–400	Completed	11		11	Treament Resistant

[a] S = Safety, DB–P = Double–Blind Parallel, OL = Open–Label, LTC = Long–Term Continuation, C = Crossover, RE = Responder Enriched.
[b] PBO = placebo
[c] b.i.d. = twice a day, q.d. = once a day, cap = capsule, C–D = chewable/dispersible, tab = compressed tablet.
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[g] US 41 is the long term continuation of US 40, US 44, and for US patients in UK 123.

Table of All Studies
Summary of Key Characteristics of Clinical Studies Included in Indication 1 – Treatment of Lennox–Gastaut Syndrome (continued)

Protocol Number	Study[a]		Control[b] (daily dose mg/day)	LAMICTAL Treatment			Completion Status	No. Entered	Age Range (yrs)	Number Exposed to LTG	Patient Type
	Objective	Design		Regimen/ formulation[c]	Duration (weeks)	Doses (mg/day)					
UK 102	S	OL	None	b.i.d. cap	4 (escalation) 44 (maintenance) 4 (taper off) Total 52	6.25–700	Completed	201		201	Treatment Resistant
UK 114[f]	S	OL LTC	None	b.i.d. cap, CD	120	12.5 – 700	Completed	133		133	Treatment Resistant
Studies Sponsored by Local Operating Companies											
UK 9001 (France)	PK, S	OL	None	q.d./b.i.d. cap	4 (escalation) 44 (maintenance) Total 48	12.5–400	Completed	27		27	Treatment Resistant
JP 01 (Japan)	S	OL	None	q.d./b.i.d. CD	4 (escalation) 8 (maintenance) 3 (taper off) Total 15	0.2–15 (mg/kg)	Completed	74		74	Treatment Resistant

[a] S = Safety, DB–P = Double–Blind Parallel, OL = Open–Label, LTC = Long–Term Continuation, C = Crossover, RE = Responder Enriched.
[b] PBO = placebo
[c] b.i.d. = twice a day, q.d. = once a day, cap = capsule, C–D = chewable/dispersible, tab = compressed tablet.
[d] VPA = sodium valproate.
[e] UK 611 is the long term continuation of UK 61.
[f] UK 114 is the long term continuation of UK 73, UK 98, and UK 102. The long–term continuation patients for UK 92 are included although they were continued in the primary study by an amendment instead of entering study UK 114.
[g] US 41 is the long term continuation of US 40, US 44, and for US patients in UK 123.

Table of All Studies
Summary of Key Characteristics of Clinical Studies Included in Indication 1 – Treatment of Lennox–Gastaut Syndrome (continued)

Protocol Number	Study[a]		Control[b] (daily dose mg/day)	LAMICTAL Treatment			Completion Status	No. Entered	Age Range (yrs)	Number Exposed to LTG	Patient Type
	Objec-tive	Design		Regimen/ formulation[c]	Duration (weeks)	Doses (mg/day)					
Ongoing Study											
UK 504 (France)	S	OL	None	q.d./b.i.d. cap, CD	6 (baseline) 4(escalation) 16 (maintenance) 2–4 (taper off) 28–30 (total)	5 – 600	Ongoing	17		17	Lennox–Gastaut syndrome
US 26	S	OL	None	b.i.d. tab	156	5–700	Ongoing	1084 (334 peds)	≥3	1084	Treatment Resistant
US 40	S, E, PK	DB–P	PBO	b.i.d. CD	4 (screen) 8 (baseline) 18 (treatment) 2–5(taper) Total 28–35	5 – 750	Ongoing	176		88	Partial Seizures
US 44	S, E	RE	PBO	b.i.d. CD	24 h (baseline) 4–10 (OL treatment) 4 (DB treatment) 1 (transition) Total 10–15	5 – 700	Ongoing	16		16	Newly Diagnosed Absence Seizures
US 418	S	OL LTC	None	q.d./b.i.d. CD	~104	5 – 750	Ongoing	94	>2	94	

[a] S = Safety, DB–P = Double–Blind Parallel, OL = Open–Label, LTC = Long–Term Continuation, C = Crossover, RE = Responder Enriched.
[b] PBO = placebo
[c] b.i.d. = twice a day, q.d. = once a day, cap = capsule, C–D = chewable/dispersible, tab = compressed tablet.
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[g] US 41 is the long term continuation of US 40, US 44, and for US patients in UK 123.

2.0 Deaths

2.1 NDA Database

There were 3 deaths reported in the NDA database. One occurred in UK 102, while 2 occurred in UK 114. The deaths are summarized below:

* Pt 114-3-308, a 13-year-old female was living in a residential epilepsy center and died at home during a holiday break. The investigator classified the death as a sudden unexplained death in epilepsy (SUDEP). The patient had been on Lamictal for 138 weeks and was on concomitant NZP and ESM. No autopsy was performed.

* Pt 114-4-403, an 8-year-old male with moderate learning disability and a 7-year history of nocturnal tonic-clonic seizures (6 per month). The patient experienced a typical seizure with some choking. Later, the child appeared to be asleep, but was found without a pulse when checked again 30 minutes later. An autopsy indicated that the likely cause of death was aspiration of gastric contents. The patient had been on Lamictal for 830 days without concomitant medications.

* Pt 102-52-5203, a 3-year-old male was classified as a SUDEP. The patient had been on Lamictal for 200 days with concomitant phenobarbital and carbamazepine. The child had been hospitalized for weight loss, but this was resolving and the child had returned home. The child was found dead in bed. An autopsy revealed no specific cause of death.

2.2 Other Sources of Information

Three deaths were reported in US 26:

* Pt US 26-2-1, a 7-year-old female, died of systemic complications 22 days after the start of Lamictal. Twelve days after starting Lamictal with concomitant VPA, she developed fever, hair loss, and a macular rash. Labs showed an elevated white cell count and elevated liver enzymes. The next day she had a diffuse macular rash, ulcers in the mouth, and conjunctivitis, all of which was attributed to a Coxsackie virus. Lamictal was continued for another day or two, until she was admitted to the hospital with vomiting, dehydration, and increased seizures. She was thought to have viral meningitis. Lamictal was stopped. The rash and

conjunctivitis were improving by the next day, but the patient's condition worsened with respiratory distress and bilateral pleural effusions. Four days after admission, she went into a coma and died 3 days later. The cause of death was thought to be viral encephalitis. An autopsy demonstrated the presence of hanta virus and chlamydia.

* Pr 26-3-4, a 4-year-old female was found dead in bed. She had been taking Lamictal for over a year. There was some indication she may have had a seizure during the night.

* Pt 26-51-39, a 14-month-old male with severe epilepsy had 2 bouts of status epilepticus, each longer than 3 hours. He then developed rhabdomyolysis, followed by shock and death.

Eleven "named" patients died. Six of the deaths were related to underlying epilepsy. Two died of pneumonia and progressive encephalopathy. One died following heart surgery. For two deaths, details are not known.

There was one death in studies by "local operating companies." The patient drowned, having been on Lamictal for almost one year.

There were no deaths in ongoing pediatric trials.

There are nine report of deaths in post-marketing surveillance. Five were complications after status epilepticus. Details of one death are unavailable One died from sepsis; one died from disseminated varicella; and one died from cardiac arrest, having been hospitalized for SJS:

* An 8-year-old boy on vigabatrin and clobazam was admitted with SJS and fever. The child developed acute renal failure treated with dialysis. The child was discharged after 45 days, but was readmitted 2 weeks later with fever and sore throat. Unexpectedly, that night, the child had a cardiac arrest and died. Autopsy revealed granuloma in the myocardium.

In Volume 2 of the January safety update (page 109), there is a report of a pediatric death from TEN occurring in post-marketing surveillance, but previously inadvertently omitted from the Glaxo database:

* A 12 year-old female was admitted with TEN 27 days after starting Lamictal. Her only other concomitant AED was carbamazepine. Lamictal was discontinued and steroids were initiated. The rash responded to steroid treatment, but she died of bilateral pneumonia and adult respiratory distress syndrome (ARDS).

Also reported in the safety update were 3 additional deaths from post-marketing surveillance between January 1, 1996 and August 31, 1996. One of the deaths was a premature infant with multiple congenital anomalies who was exposed to Lamictal for the first 6 weeks of gestation. There are few details for one of the deaths which was listed as due to pneumonia. The third death is described below:

* A 7 year-old male received Lamictal and presented to the hospital in status epilepticus (the duration of Lamictal exposure is unknown). While in the hospital, the child remained unconscious, became hemodynamically unstable, and then developed liver failure. He developed multiple organ failure and began dialysis. He died 2 days after dialysis and after 5 days of hospitalization. The physician thought that the multiple organ failure may have been possibly caused by Lamictal.

3.0 Dropouts

In the open-label studies, n=320, 179 (56%) discontinued medication prematurely. The reasons given were adverse events (13%), inadequate response (28%), and administrative reasons (9%). In UK 123, 7 pts (9%) discontinued in the Lamictal group vs. 14 pts (16%) in the placebo group. 4% of Lamictal pts vs 8% of placebo pts discontinued for AEs.

Of the 399 pts in the NDA database, 46 (11.5%) discontinued because of an AE. When all rash-related terms are combined, the incidence of rash-related discontinuations was 6% (24 of 399 pts). Other events experienced by more than 1 patient that contributed to discontinuation were reaction aggravated (8 pts), ataxia (4 pts), agitation (3 pts), fever (2 pts), and vomiting (2 pts). All other AEs contributing to discontinuation were experienced by one patient each. Sponsor's Table 5.44 tabulates AEs leading to discontinuation.

Table 5.44
Incidence of Adverse Experiences Leading to Discontinuation of
LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N-399)				
		Patients		Number of Patients with Maximum Intensity		
		No.	% [1]	Mild	Moderate	Severe
Total No. of Patients Discontinued due to AEs		46	11.5%	10	18	18
General	REACT AGGRAV	8	2.0%	1	5	2
	FEVER	2	0.5%	1	0	1
	ASTHENIA	1	0.3%	0	1	0
	HEADACHE	1	0.3%	1	0	0
	REACT UNEVAL	1	0.3%	0	1	0
Nervous System	ATAXIA	4	1.0%	1	1	2
	AGITATION	3	0.8%	0	1	2
	AKATHISIA	1	0.3%	1	0	0
	CONFUS	1	0.3%	0	1	0
	COORDINAT ABNORM	1	0.3%	0	0	1
	DYSARTHRIA	1	0.3%	0	0	1
	EDEMA BRAIN	1	0.3%	0	0	1
	EEG ABNORM	1	0.3%	0	0	1
	EMOTION LABIL	1	0.3%	0	0	1
	HOSTILITY	1	0.3%	0	0	1
	HYPERKINESIA	1	0.3%	0	0	1
	HYPERTONIA	1	0.3%	1	0	0
	NERVOUSNESS	1	0.3%	0	1	0
	PARESTHESIA	1	0.3%	0	0	1
	SOMNOLENCE	1	0.3%	0	0	1
	THINKING ABNORM					
Respiratory	EPISTAXIS	1	0.3%	1	0	0
	HYPERVENTIL	1	0.3%	0	1	0
	LUNG DISORDER	1	0.3%	0	1	0
	PHARYNGITIS	1	0.3%	1	0	0
Digestive	VOMIT	2	0.5%	0	2	0
	CONSTIP	1	0.3%	0	1	0
Skin	RASH	18	4.5%	4	8	6
	RASH MAC PAP	5	1.3%	2	1	2
	ALOPECIA	1	0.3%	0	0	1
	ECZEMA	1	0.3%	1	0	0
	HIRSUTISM	1	0.3%	0	0	1

[1] Percentage is calculated using the overall number of LAMICTAL Patients (N-399) as the denominator.

NOTE: Patient 123-2009 discontinued from LAMICTAL therapy with an AE that was not treatment emergent.
Patient 092-5003 discontinued from the study due to increased seizure frequency reported as an AE, but the termination record recorded the reason for discontinuation as 'Other'.

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Incidence of Adverse Experiences Leading to Discontinuation of
LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399)				
		Patients		Number of Patients with Maximum Intensity		
		No.	% [1]	Mild	Moderate	Severe
Skin	STEVENS JOHNSON SYND	1	0.3%	0	0	1
Hemic & Lymphatic	LEUKOPENIA	1	0.3%	0	1	0
	LYMPHADENO	1	0.3%	1	0	0
Metabolic & Nutritional	CREATININE INC	1	0.3%	0	1	0
	EDEMA	1	0.3%	0	1	0
	EDEMA PERIPH	1	0.3%	0	1	0
Musculoskeletal	SPASM GENERAL	1	0.3%	0	1	0

[1] Percentage is calculated using the overall number of LAMICTAL Patients (N=399) as the denominator.
NOTE: Patient 123-2009 discontinued from LAMICTAL therapy with an AE that was not treatment emergent.
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