4.0 All Adverse Events

The treatment-emergent AEs in the NDA database are all listed in Sponsor's Table 5.29.

Sponsor's Table 5.32 summarizes the AEs from the controlled trial, UK 123. Sponsor's Table 5.38 summarizes the AEs from UK 123 that occurred ≥ 1% of patients in the Lamictal group and more frequently than the placebo group.

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Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences
on LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399) Patients No.	Patients % [1]	Number of Patients with Maximum Intensity [2] Mild	Moderate	Severe
Total No. of Patients with Adverse Experiences		316	79.2%	86	167	63
General	REACT AGGRAV	58	14.5%	12	33	10
	INFECT	51	12.8%	36	13	2
	FEVER	46	11.5%	27	16	2
	HEADACHE	29	7.3%	21	6	2
	REACT UNEVAL	25	6.3%	7	15	2
	ASTHENIA	21	5.3%	9	12	0
	INJURY ACCID	17	4.3%	10	4	2
	FLU SYND	14	3.5%	12	2	0
	PAIN ABDO	12	3.0%	9	3	0
	PAIN	7	1.8%	5	2	0
	ALLERG REACT	3	0.8%	0	3	0
	HALITOSIS	2	0.5%	1	1	0
	UNEXPECTED BENEFIT	2	0.5%	1	1	0
	CELLULITIS	1	0.3%	0	0	1
	CHILLS	1	0.3%	1	0	0
	EDEMA FACE	1	0.3%	1	0	0
	LAB TEST ABNORM	1	0.3%	1	0	0
	MALAISE	1	0.3%	1	0	0
	NEOPL	1	0.3%	0	1	0
	OVERDOSE ACCID	1	0.3%	0	1	0
	PAIN BACK	1	0.3%	0	1	0
	SEPSIS	1	0.3%	0	1	0
Nervous System	SOMNOLENCE	62	15.5%	33	25	4
	ATAXIA	26	6.5%	7	13	6
	HYPERKINESIA	20	5.0%	5	14	1
	NERVOUSNESS	17	4.3%	11	6	0
	TREMOR	17	4.3%	7	9	1
	HOSTILITY	15	3.8%	7	6	2
	INSOMNIA	15	3.8%	6	9	0
	DIZZINESS	14	3.5%	10	3	1
	PERSON DISORDER	11	2.8%	3	8	0
	THINKING ABNORM	9	2.3%	5	3	1
	AGITATION	8	2.0%	3	3	2
	EMOTION LABIL	8	2.0%	4	3	1

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=399) 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=232) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=167) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences
on LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	% [1]	Mild	Moderate	Severe
Nervous System	AKATHISIA	5	1.3%	2	1	2
	CNS DEPRESS	5	1.3%	5	0	0
	HYPERTONIA	5	1.3%	1	3	1
	CONFUS	4	1.0%	1	3	0
	COORDINAT ABNORM	4	1.0%	2	1	1
	DYSARTHRIA	4	1.0%	2	1	1
	GAIT ABNORM	4	1.0%	3	0	1
	VERTIGO	4	1.0%	3	1	0
	CONVULS	3	0.8%	2	1	0
	HYPOTONIA	3	0.8%	1	1	1
	CNS STIMULAT	2	0.5%	2	0	0
	DEPRESSION	2	0.5%	1	1	0
	DREAM ABNORM	2	0.5%	0	2	0
	HALLUCIN	2	0.5%	1	1	0
	PARALYSIS FACIAL	2	0.5%	1	1	0
	SLEEP DISORDER	2	0.5%	1	1	0
	SPEECH DISORDER	2	0.5%	0	1	1
	AMNESIA	1	0.3%	1	0	0
	ANXIETY	1	0.3%	0	1	0
	APHASIA	1	0.3%	0	1	0
	CEREBELL SYND	1	0.3%	1	0	0
	CHOREOATHETOSIS	1	0.3%	1	0	0
	CONVULS GRAND MAL	1	0.3%	0	1	0
	DYSTONIA	1	0.3%	0	1	0
	EDEMA BRAIN	1	0.3%	0	0	1
	EEG ABNORM	1	0.3%	0	0	1
	MENTAL RETARD	1	0.3%	1	0	0
	MYOCLONUS	1	0.3%	0	1	0
	NEUROSIS	1	0.3%	0	1	0
	PARESTHESIA	1	0.3%	0	1	0
	STUPOR	1	0.3%	0	1	0
Respiratory	PHARYNGITIS	51	12.8%	35	14	1
	RHINITIS	29	7.3%	24	5	0
	RESPIRAT DISORDER	25	6.3%	13	11	0
	BRONCHITIS	20	5.0%	11	8	1
	COUGH INC	11	2.8%	9	2	0
	LUNG DISORDER	7	1.8%	4	2	1

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=399) 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=232) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=167) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences
on LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	% [1]	Mild	Moderate	Severe
Respiratory	EPISTAXIS	4	1.0%	2	2	0
	PNEUMONIA	4	1.0%	0	3	1
	SINUSITIS	3	0.8%	1	2	0
	BRONCHOSPASM	2	0.5%	1	1	0
	DYSPNEA	2	0.5%	2	0	0
	APNEA	1	0.3%	0	1	0
	HYPERVENTIL	1	0.3%	0	1	0
Digestive	VOMIT	54	13.5%	30	23	1
	DIARRHEA	15	3.8%	9	6	0
	NAUSEA	15	3.8%	13	2	0
	SALIVA INC	15	3.8%	8	6	1
	ANOREXIA	11	2.8%	5	5	1
	CONSTIP	10	2.5%	6	3	1
	GASTROENTERITIS	5	1.3%	2	3	0
	TOOTH DISORDER	3	0.8%	1	1	1
	GASTRITIS	2	0.5%	2	0	0
	ULCER MOUTH	2	0.5%	1	0	0
	APPETITE INC	1	0.3%	0	1	0
	DYSPEPSIA	1	0.3%	0	1	0
	GINGIVITIS	1	0.3%	1	0	0
	STOMATITIS APHTH	1	0.3%	0	1	0
	THIRST	1	0.3%	1	0	0
Skin	RASH	49	12.3%	28	14	7
	RASH MAC PAP	12	3.0%	7	3	2
	ECZEMA	10	2.5%	8	2	0
	HERPES ZOSTER	5	1.3%	3	2	0
	ALOPECIA	3	0.8%	1	1	1
	FURUNCULOSIS	3	0.8%	2	1	0
	RASH VESIC BULL	3	0.8%	3	0	0
	ACNE	2	0.5%	2	0	0
	HIRSUTISM	2	0.5%	0	0	2
	PRURITUS	2	0.5%	1	1	0
	SKIN DISORDER	2	0.5%	1	1	0
	HAIR DISORDER	1	0.3%	1	0	0
	HERPES SIMPLEX	1	0.3%	0	0	1
	NAIL DISORDER	1	0.3%	1	0	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=399) 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=232) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=167) as the denominator.

Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences
on LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399)				
		Patients		Number of Patients with Maximum Intensity[2]		
		No.	% [1]	Mild	Moderate	Severe
Skin	SKIN DRY	1	0.3%	1	0	0
	STEVENS JOHNSON SYND	1	0.3%	0	0	1
	URTICARIA	1	0.3%	0	1	0
Special Senses	EAR DISORDER	9	2.3%	7	2	0
	OTITIS MED	9	2.3%	4	5	0
	DIPLOPIA	5	1.3%	3	1	1
	CONJUNCTIVITIS	4	1.0%	3	1	0
	PAIN EAR	3	0.8%	3	0	0
	BLURRED VISION	2	0.5%	1	1	0
	VISION ABNORM	2	0.5%	1	1	0
	BLEPHARITIS	1	0.3%	0	1	0
	KERATITIS	1	0.3%	0	0	1
	OTITIS EXT	1	0.3%	0	1	0
	PAIN EYE	1	0.3%	1	0	0
	PHOTOPHOBIA	1	0.3%	0	1	0
	STRABISMUS	1	0.3%	1	0	0
	TASTE PERVERS	1	0.3%	1	0	0
Urogenital	INFECT URIN TRACT	6	1.5%	2	4	0
	INCONTIN URIN	4	1.0%	2	2	0
	PYELONEPHRITIS	2	0.5%	2	0	0
	URIN RETENT	2	0.5%	1	1	0
	BALANITIS[3]	1	0.4%	1	0	0
	CYSTITIS	1	0.3%	1	0	0
	DYSMENORRHEA[4]	1	0.6%	0	1	0
	PENIS DISORDER[3]	1	0.4%	1	0	0
	POLYURIA	1	0.3%	1	0	0
	SEX MAT ACCEL	1	0.3%	1	0	0
	URIN FREQUENCY	1	0.3%	0	1	0
Hemic & Lymphatic	ANEMIA	7	1.8%	4	2	1
	LYMPHADENO	4	1.0%	3	1	0
	LEUKOPENIA	3	0.8%	2	1	0
	ANEMIA IRON DEFIC	1	0.3%	1	0	0
	EOSINOPHILIA	1	0.3%	1	0	0
	LEUKOCYTOSIS	1	0.3%	1	0	0
	PLAT ABNORM	1	0.3%	1	0	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=399) 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=232) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=167) as the denominator.

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Table 5.29
Overall Incidence of Treatment Emergent Adverse Experiences
on LAMICTAL Treatment in All Pediatric Studies

Body System	Preferred Adverse Experience Term	LAMICTAL Patients (N=399) Patients No.	% [1]	Number of Patients with Maximum Intensity [2] Mild	Moderate	Severe
Hemic & Lymphatic	THROMBOCYTOPENIA	1	0.3%	0	0	1
Metabolic & Nutritional	WEIGHT INC	6	1.5%	4	1	1
	WEIGHT DEC	3	0.8%	1	2	0
	EDEMA	2	0.5%	1	1	0
	OBESITY	2	0.5%	0	2	0
	CREATININE INC	1	0.3%	0	0	1
	EDEMA PERIPH	1	0.3%	0	1	0
	SGOT INC	1	0.3%	0	1	0
	SGPT INC	1	0.3%	1	0	0
Cardiovascular	PALLOR	3	0.8%	1	2	0
	HEMORR	2	0.5%	2	0	0
	ANGINA PECTORIS	1	0.3%	1	0	0
	VASC DISORDER PERIPH	1	0.3%	1	0	0
	VASODILAT	1	0.3%	1	0	0
Musculoskeletal	TWITCH	2	0.5%	0	1	1
	ARTHRITIS	1	0.3%	1	0	0
	MYALGIA	1	0.3%	1	0	0
	MYASTHENIA	1	0.3%	1	0	0
	OSTEOMYELITIS	1	0.3%	0	1	0
	SPASM GENERAL	1	0.3%	0	1	0
Endocrine	HYPOTHYR	2	0.5%	2	0	0
	CUSHINGS SYND	1	0.3%	0	1	0

[1] Percentage is calculated using the overall number of LAMICTAL patients (N=399) 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=232) as the denominator.
[4] Percentage is calculated using the overall number of female LAMICTAL patients (N=167) as the denominator.

Table 5.32
Summary of Treatment Emergent Adverse Experience Rates in UK123

Body System Adverse Experience	LAMICTAL (N-79) No. (%) of Pts	LAMICTAL (N-79) No. of Pts. with Maximum Intensity Mild	Mod	Sev	Placebo (N-90) No. (%) of Pts	Placebo (N-90) No. of Pts. with Maximum Intensity Mild	Mod	Sev	Between Treatment Comparison Diff. in Prop.	95% C.I.
GENERAL	34 (43)				35 (39)					
FEVER	10 (13)	8	2	0	12 (13)	10	2	0	0.00	(-0.102, 0.102)
INFECT	10 (13)	9	0	1	7 (8)	6	1	0	0.05	(-0.043, 0.143)
INJURY ACCID	7 (9)	6	1	0	6 (7)	5	1	0	0.02	(-0.062, 0.102)
FLU SYND	4 (5)	4	0	0	0 (0)	0	0	0	0.05	(0.002 , 0.098)
HEADACHE	3 (4)	2	0	1	6 (7)	5	1	0	-0.03	(-0.098, 0.038)
REACT AGGRAV	3 (4)	1	2	0	7 (8)	2	2	3	-0.04	(-0.111, 0.031)
ASTHENIA	2 (3)	0	2	0	1 (1)	1	0	0	0.02	(-0.023, 0.063)
PAIN ABDO	2 (3)	1	1	0	0 (0)	0	0	0	0.03	(-0.008, 0.068)
UNEXPECTED BENEFIT	2 (3)	1	1	0	0 (0)	0	0	0	0.03	(-0.008, 0.068)
EDEMA FACE	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
LAB TEST ABNORM	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
PAIN	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
PAIN BACK	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
INFECT RESPIRAT TRACT	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
PAIN CHEST	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
REACT UNEVAL	0 (0)	0	0	0	3 (3)	3	0	0	-0.03	(-0.065, 0.005)
NERVOUS SYSTEM	17 (22)				15 (17)					
ATAXIA	3 (4)	1	1	1	1 (1)	1	0	0	0.03	(-0.018, 0.078)
CONVULS	3 (4)	2	1	0	1 (1)	0	1	0	0.03	(-0.018, 0.078)
SOMNOLENCE	3 (4)	1	2	0	4 (4)	3	1	0	0.00	(-0.059, 0.059)
INSOMNIA	2 (3)	1	1	0	3 (3)	2	1	0	0.00	(-0.052, 0.052)
TREMOR	2 (3)	0	1	1	0 (0)	0	0	0	0.03	(-0.008, 0.068)
AGITATION	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
CONVULS GRAND MAL	1 (1)	0	1	0	2 (2)	1	1	0	-0.01	(-0.046, 0.026)
COORDINAT ABNORM	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
DIZZINESS	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
EMOTION LABIL	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
HOSTILITY	1 (1)	0	1	0	1 (1)	1	0	0	0.00	(-0.030, 0.030)
HYPERKINESIA	1 (1)	0	1	0	1 (1)	0	1	0	0.00	(-0.030, 0.030)
NERVOUSNESS	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
VERTIGO	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
GAIT ABNORM	0 (0)	0	0	0	1 (1)	0	1	0	-0.01	(-0.031, 0.011)
HYPOTONIA	0 (0)	0	0	0	1 (1)	0	0	1	-0.01	(-0.031, 0.011)
IRRITABILITY	0 (0)	0	0	0	2 (2)	0	2	0	-0.02	(-0.049, 0.009)
MYOCLONUS	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
THINKING ABNORM	0 (0)	0	0	0	1 (1)	0	1	0	-0.01	(-0.031, 0.011)
RESPIRATORY	23 (29)				21 (23)					
PHARYNGITIS	11 (14)	7	4	0	9 (10)	8	1	0	0.04	(-0.058, 0.138)
BRONCHITIS	7 (9)	2	4	1	6 (7)	2	3	1	0.02	(-0.062, 0.102)

[1] Male specific adverse experience. (LTG, N-54; PBO, N-45)
[2] Female specific adverse experience. (LTG, N-25; PBO, N-45)

Table 5.32
Summary of Treatment Emergent Adverse Experience Rates in UK123

Body System Adverse Experience	LAMICTAL (N=79) No. (%) of Pts	LAMICTAL (N=79) No. of Pts. with Maximum Intensity: Mild	Mod	Sev	Placebo (N=90) No. (%) of Pts	Placebo (N=90) No. of Pts. with Maximum Intensity: Mild	Mod	Sev	Between Treatment Comparison: Diff. in Prop.	95% C.I.
RHINITIS	4 (5)	4	0	0	7 (8)	6	1	0	-0.03	(-0.104, 0.044)
COUGH INC	2 (3)	1	1	0	3 (3)	3	0	0	0.00	(-0.052, 0.052)
PNEUMONIA	2 (3)	0	2	0	0 (0)	0	0	0	0.03	(-0.008, 0.068)
DYSPNEA	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
LUNG DISORDER	1 (1)	1	0	0	1 (1)	0	1	0	0.00	(-0.030, 0.030)
SINUSITIS	1 (1)	1	0	0	1 (1)	1	0	0	0.00	(-0.030, 0.030)
EPISTAXIS	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
DIGESTIVE	17 (22)				13 (14)					
VOMIT	7 (9)	5	1	1	6 (7)	5	1	0	0.02	(-0.062, 0.102)
CONSTIP	4 (5)	3	1	0	2 (2)	2	0	0	0.03	(-0.026, 0.086)
DIARRHEA	3 (4)	3	0	0	2 (2)	2	0	0	0.02	(-0.032, 0.072)
NAUSEA	3 (4)	3	0	0	1 (1)	1	0	0	0.03	(-0.018, 0.078)
ANOREXIA	2 (3)	2	0	0	1 (1)	0	1	0	0.02	(-0.023, 0.063)
GASTROENTERITIS	1 (1)	0	1	0	1 (1)	0	1	0	0.00	(-0.030, 0.030)
STOMATITIS APHTH	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
TOOTH DISORDER	1 (1)	0	0	1	0 (0)	0	0	0	0.01	(-0.012, 0.032)
DYSPEPSIA	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
HYPER GUM	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
LIVER FUNC ABNORM	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
SKIN	11 (14)				7 (8)					
RASH	7 (9)	4	1	2	4 (4)	3	1	0	0.05	(-0.025, 0.125)
ECZEMA	3 (4)	3	0	0	0 (0)	0	0	0	0.04	(-0.003, 0.083)
ACNE	1 (1)	1	0	0	1 (1)	1	0	0	0.00	(-0.030, 0.030)
NAIL DISORDER	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
RASH PUST	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
RASH VESIC BULL	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
SPECIAL SENSES	5 (6)				5 (6)					
BLEPHARITIS	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
CONJUNCTIVITIS	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
KERATITIS	1 (1)	0	0	1	0 (0)	0	0	0	0.01	(-0.012, 0.032)
OTITIS MED	1 (1)	1	0	0	4 (4)	3	1	0	-0.03	(-0.076, 0.016)
PAIN EAR	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
PAIN EYE	1 (1)	1	0	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
EYE DISORDER	0 (0)	0	0	0	1 (1)	1	0	0	-0.01	(-0.031, 0.011)
UROGENITAL	3 (4)				2 (2)					
INFECT URIN TRACT	2 (3)	0	2	0	0 (0)	0	0	0	0.03	(-0.008, 0.068)
BALANITIS[1]	1 (2)	1	0	0	0 (0)	0	0	0	0.02	(-0.017, 0.057)
PENIS DISORDER[1]	1 (2)	1	0	0	0 (0)	0	0	0	0.02	(-0.017, 0.057)

[1] Male specific adverse experience. (LTG, N=54; PBO, N=45)
[2] Female specific adverse experience. (LTG, N=25; PBO, N=45)

Table 5.32
Summary of Treatment Emergent Adverse Experience Rates in UK123

Body System Adverse Experience	LAMICTAL (N=79)				Placebo (N=90)				Between Treatment Comparison	
	No. (%) of Pts	No. of Pts. with Maximum Intensity			No. (%) of Pts	No. of Pts. with Maximum Intensity			Diff. in Prop.	95% C.I.
		Mild	Mod	Sev		Mild	Mod	Sev		
INCONTIN URIN	0 (0)	0	0	0	2 (2)	2	0	0	-0.02	(-0.049, 0.009)
HEMIC & LYMPHATIC	1 (1)				1 (1)				0.01	(-0.012, 0.032)
LYMPHADENO	1 (1)	1	0	0	0 (0)	0	0	0	-0.01	(-0.031, 0.011)
THROMBOCYTOPENIA	0 (0)	0	0	0	1 (1)	0	0	1		
METABOLIC & NUTRITIONAL	1 (1)				1 (1)				0.00	(-0.030, 0.030)
WEIGHT INC	1 (1)	1	0	0	1 (1)	1	0	0		
CARDIOVASCULAR	2 (3)				0 (0)				0.03	(-0.008, 0.068)
HEMORR	2 (3)	2	0	0	0 (0)	0	0	0		
MUSCULOSKELETAL	0 (0)				1 (1)				-0.01	(-0.031, 0.011)
ARTHRALGIA	0 (0)	0	0	0	1 (1)	1	0	0		
ENDO	2 (3)				0 (0)				0.01	(-0.012, 0.032)
CUSHINGS SYND	1 (1)	0	1	0	0 (0)	0	0	0	0.01	(-0.012, 0.032)
HYPOTHYR	1 (1)	1	0	0	0 (0)	0	0	0		

1 Male specific adverse experience. (LTG, N=54; PBO, N=45)
2 Female specific adverse experience. (LTG, N=25; PBO, N=45)

Table 5.38. **Treatment–Emergent Adverse Event Incidence in Placebo–Controlled Add–on Trial in Children and Adults With Lennox–Gastaut Syndrome. (Events in at least 1% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)**

Body System/Adverse Experience	Percent of Patients Receiving LAMICTAL (n=79)	Percent of Patients Receiving Placebo (n=90)
BODY AS A WHOLE	13	8
Infection	9	7
Accidental Injury	5	0
Flu Syndrome	3	1
Asthenia	3	0
Abdominal Pain	1	0
Back Pain	1	0
Edema of the Face	1	0
Lab Test Abnormal	1	0
Pain		
CARDIOVASCULAR	3	0
Hematoma		
DIGESTIVE	9	7
Vomiting	5	2
Constipation	4	2
Diarrhea	4	1
Nausea	3	1
Anorexia	1	0
Stomatitis Aphthous	1	0
Tooth Disorder		
ENDOCRINE	1	0
Cushing's Syndrome	1	0
Hypothyroidism		
HEMIC AND LYMPHATIC	1	0
Lymphadenopathy		
NERVOUS SYSTEM	4	1
Ataxia	4	1
Convulsions	3	0
Tremor	1	0
Agitation	1	0
Coordination	1	0
Dizziness	1	0
Emotional Lability	1	0
Nervousness	1	0
Vertigo		

Table 5.38. Treatment–Emergent Adverse Event Incidence in Placebo–Controlled Add–on Trial in Children and Adults With Lennox–Gastaut Syndrome. (Events in at least 1% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.) (continued)

Body System/Adverse Experience	Percent of Patients Receiving LAMICTAL (n=79)	Percent of Patients Receiving Placebo (n=90)
RESPIRATORY		
Pharyngitis	14	10
Bronchitis	9	7
Pneumonia	3	0
Dyspnea	1	0
SKIN		
Rash	9	7
Eczema	4	0
Nail Disorder	1	0
SPECIAL SENSES		
Blepharitis	1	0
Conjunctivitis	1	0
Keratitis	1	0
Ear Pain	1	0
Eye Pain	1	0
UROGENITAL		
Urinary Tract Infection	3	0
Balanitis	2	0
Penis Disorder	2	0

5.0 Severe Cutaneous Adverse Reactions

Surprisingly, the ISS for this Lamictal CD NDA does not contain a comprehensive review of SJS/TEN in pediatric populations, even though the high risk of SJS/TEN has clearly become the primary safety concern with Lamictal use. The sponsor's tables already presented only reflect a single case of SJS out of 399 patients in the pediatric NDA database.

The main safety concern with Lamictal is the risk of severe, potentially life-threatening rash, to include Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Both are full-thickness, desquamating rashes, with or without mucosal involvement, and with the potential to be life-threatening. If viewed as a continuum, SJS would involve 10% of body surface area or less, while TEN would involve 30% of body surface area or more. The SJS/TEN Overlap Syndrome encompasses 10-30% body surface area. Obviously, the greater the surface area involved, the more serious the situation, and the more life-threatening the rash. SJS is thought to carry a mortality of 5% or less while TEN may carry a mortality of 30%.

Commonly used AEDs such as carbamazepine and phenytoin are generally believed to carry a risk of SJS of 1/5000 to 1/10000. At the time of approval in this country, 2-3 cases of SJS had occurred in an NDA database of 3000 patients (predominantly adults). Because the size of the database was relatively small, the confidence intervals for the risk estimate were wide.

In fact, while the Lamictal NDA was under review in early 1994 in the US, the first year of post-marketing experience in Germany (1993) suggested a risk as high as 1/250 for SJS/TEN.

At that time, the sponsor looked at preliminary evidence suggesting that starting dose and rate of dose escalation predicted risk of mild rash with Lamictal. In patients on VPA monotherapy, the institution of Lamictal at a dose of 50mg bid was associated with a risk of mild rash of almost 50%. Starting doses of 25mg qd and 25mg qod vastly improved the situation and 25mg qod was adopted as the Lamictal starting dose in adults with any

concomitant VPA.[1] This entailed a change in dosing guidelines in Europe, but became part of the original approved labeling in this country.[2]

Also, while the Lamictal NDA was under review in the U.S., it was noted from European post-marketing experience that concomitant VPA use seemed disproportionately high among patients who developed SJS/TEN. Labeling in the U.S. comments on this point.

During the first 2 years of marketing in the U.S. (1995 and 1996), post-marketing reports of SJS/TEN in children began to appear. A DEAR DOCTOR letter was sent out in early 1995 when 2 children, given doses equal to or greater than the recommended adult dose, developed severe rashes.

In the interest of defining the risk of serious cutaneous adverse reports (SCAR) with Lamictal in early 1996, DNDP consulted the epidemiology division. Dooley, et al[3] had reported in January 1996 on a cohort of patients who "represent all children treated with lamotrigine in Nova Scotia between 1990 and 1994." Five of 68 consecutively treated children developed rash. One was SJS or TEN. Thus, the risk estimate was 1/68 in this primarily pediatric cohort. Three/68 cases were hospitalized

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[1]Note that if the belief was that rash was related to plasma levels of lamotrigine, knowledge about the effect of VPA vs VPA+EIAED on lamotrigine kinetics would suggest that a starting dose of Lamictal 25mg qod with VPA alone (lamotrigine half-life 12 hours) should be distinguished from a starting dose of 50mg qod with VPA+EIAED (lamotrigine half-life 24 hours). In early 1994, the more conservative approach was adopted, i.e. using the same low starting dose of Lamictal with concomitant VPA (whether or not there was an associated concomitant EIAED).

[2]Lamictal was only approved for use in adults in the U.S. In countries where pediatric use was approved, the 25mg qod starting dose corresponded to 0.2mg/kg/day in children.

[3]Dooley, Camfield, Gordon, et al. Lamotrigine-induced rash in children. Neurology 1996; 46: 240-242.

with rash. This followed the report by Arnold, et al[4] in 1995 in which 1/38 children treated with Lamictal developed severe SJS leaving her with corneal and conjunctival scarring, but normal visual acuity.

Dr. Davis' epidemiology review was completed even before the NDA for Lamictal CD (the pediatric dosage form) was submitted. Dr. Davis' risk estimates for rash-associated hospitalization were higher for children ≤ 14 years than for adults (8/1000 and 20/1000 were 2 estimates for children ≤ 14 years based on different assumptions about under-reporting and continued usage). He noted that since Lamictal was recently approved and is not labeled for children, health care providers might be more likely to report AEs among children (reporting bias for children). VPA appeared to elevate the risk of hospitalized rash in both adults and children, but Dr. Davis came to no conclusions on the role of dose escalation and hospitalized rash.

5.1 NDA Database

From page 53 of Integrated Summary of Safety: 4 pts reported "serious or life threatening" skin related AEs in the NDA database:

Pt.102-51-5101	Diffuse rash and edema
Pt.123-18-1802	Hospitalized with severe rash and stomatitis
Pt.123-55-5504	Severe rash and stomatitis
Pt.102-60-6009	SJS

I would include Pt.5602 from Study 123 in this list, for a total of 5. Pt 5602 was classified as an administrative discontinuation, but developed SJS shortly thereafter. This would bring to 2 the number of pediatric patients out of 399 who were given the label "SJS" in the database. "Patient 5504 was thought to have SJS, but when examined by a dermatologist, this was not confirmed conclusively."

In UK123 (n=79 pediatric pts exposed to Lamictal) Pt.5504 was never hospitalized, while patients 1802 and 5602 were hospitalized and, from the information provided, might meet the definition of SJS. Two of the 3 patients had starting doses of 0.4mg/kg/day (one of these two was not

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[4]Arnold, Bourgeois, Montouris, et al. Safety profile of lamotrigine in children. Epilepsia 1995; 36 (Suppl. 4): 67.

hospitalized); the third patient had a starting dose of 0.3mg/kg/day.

No further descriptive information on the rashes for the 2 patients in Study 102 appears to be provided in the NDA. Tabular listings do provide information on these patients for concomitant AEDs, time of onset of rash, and starting dose of Lamictal. That information is provided in the table on the next page.

Thus, there might be 2-4 cases of SJS out of 399 exposures. The sponsor was asked to provide narratives of the 5 cases discussed in this section, specifically addressing the clinical outcome for each case.

5.2 Other Sources of Information

There are 5 additional pediatric databases available, (a) through (e) below:

(a) Glaxo Wellcome's Worldwide SRS. 200,000 patients, including adults and children. There is no estimate of the proportion of these patients under age 14 years. The sponsor's database includes 25 reported cases of SJS. No sequelae were reported for 14, while outcome for the rest is unknown.

(b) Named Patients in Foreign Countries. Glaxo states that information on exposure is unavailable. A total of 17 rashes labeled "serious" were seen in this database. Further information on these does not appear to be in the NDA.

(c) Compassionate Use Protocol 26 in the US. Glaxo Wellcome does not merge this safety data with the pediatric NDA database; together Protocol 26 plus the pediatric NDA database would include 733 children. The sponsor stated that US 26 was not a closed study and that the database had not yet been locked and quality assured. For that reason, the sponsor did not feel it appropriate to merge US 26 with the quality assured NDA database.

In a November 25, 97 response to my questions about Study 26, the sponsor provided case histories of the 5 children with rashes labeled "serious" in that study (total of 334 pediatric patients). A review of those cases supports the sponsor's contention that probably none of the 5

Patients with Serious or Life-Threatening Skin Related AEs in Lamictal CD NDA Database:

Patient Number	Concomitant VPA	Onset	Starting Dose	Outcome
123-1802	Yes	Week 5	0.4mg/kg/day	Good
123-5504	Yes	Week 5	0.4mg/kg/day	Good
123-5602	Yes	Week 2-3	0.3mg/kg/day	?
102-6009	No	Week 2	2.5mg/kg/day	?
102-5101	No	Week 7	?	?

would meet the definition of SJS.

(d) and (e) The fourth source of information would be on-going pediatric trials. The fifth source of information would be what the sponsor labels "local company sponsored trials."

In one study in children included in the "local operating company" database, Study JP 01, there has been 1 labeled case of SJS among the 74 exposed. In this Japanese study, the case of SJS occurred **after 4 months**. In an ongoing study in children, Study US 40, there has already been 1 labeled case of SJS among the 88 exposed.

In the safety update, an ongoing study in Japan, JP 02, is added, reporting 1 case of SJS out of 79 patients exposed to Lamictal.

5.3 Request for BOX WARNING

Given the new information in the Lamictal CD NDA, DNDP issued a letter to the sponsor on December 17, 1996 requesting a BOX WARNING for Lamictal.

5.4 Safety Update

On January 17, 1997 the sponsor submitted a safety update which addressed the risk of rash in children (and in adults) in a much more comprehensive fashion than the NDA ISS itself. In particular, the results of 2 epidemiologic studies of rash-risk with Lamictal were presented for the first time:

The ALERT Study was a prospective study of rash in newly treated adults in the U.S. In 767 exposures, there was 1 case of SJS.

The PEM Study was a prospective study of rash performed in children and adults in the U.K. Overall, 12/11,000 developed SJS. For children alone in this PEM database, the risk of SJS was 5/1598.

5.5 Meeting With Sponsor

On February 4, 1997 the sponsor submitted a risk-reduction strategy based on their belief that the higher risk estimates for SJS/TEN emerging from pediatric databases were due to higher starting doses, faster dose

escalation, and greater concomitant VPA use in pediatric populations.

In that February 4 submission, the sponsor's evidence that appropriate dose escalation could reduce risk of SJS was derived almost entirely from lower risk estimates of SJS/TEN in Germany since the change in dosing guidelines in early 1994. However, the estimates of new exposures in recent years in Germany are not precise and, while ascertainment of cases in Germany's SCAR (severe cutaneous adverse reaction) reporting system may be better than elsewhere, there is no guarantee that case ascertainment has not systematically changed over the years.

In a meeting with the firm on February 19, 1997, the firm agreed to draft a BOX WARNING and a Dear Doctor Letter addressing the higher risk estimates that have recently emerged. Negotiations with the firm resulted in the current BOX WARNING.

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6.0 Liver Failure/Multiple Organ Failure

Liver failure and multi-organ failure (MOF) in adults are described in current labeling. They have occurred as primary events and as terminal events in systemically compromised patients following bouts of status epilepticus. Note that the lack of information over time for individual cases of liver failure and multi-organ failure may not always distinguish clearly between primary events and events secondary to status epilepticus.

Cases of multi-organ failure leading to death are included in this review in Section 2.0 Deaths. Those cases, on review, all seemed most likely to fall under the classification "secondary to status epilepticus."

In the ISS, Section 5.4.17.6, the sponsor discusses multiple organ failure/dysfunction *as defined by clinically significant abnormalities in two or more body systems.* The sponsor has maintained (and current labeling endorses this distinction in the WARNINGS section) that cases of MOF with Lamictal can be divided into a) those which occur early after exposure, have associated rash, fit the clinical picture of drug hypersensitivity syndrome, and are associated with a quick recovery when drug is withdrawn, and b) those which occur at any time after exposure, tend not to have associated rash, follow status epilepticus, and have a high mortality. Sponsor's Tables 5.74 and 5.75 tabulate cases from post-marketing surveillance that fall into these 2 categories. Note that disseminated intravascular coagulation appears often in the latter group. DIC is discussed below in Section 7.0.

Pertinent to the distinction between primary and secondary MOF, on page 85 of the ISS, the sponsor states, "Nine of the eleven patients reporting MOF without rash died; six of these suffered status epilepticus as a prelude to MOF and death." I believe this is an incorrect statement. My review of the nine deaths reveals that all nine had status epilepticus." If 3 had not suffered status epilepticus as a prelude to MOF and death, as the sponsor states, there would be real concern that Lamictal had caused those deaths.

A case of liver failure from post-marketing surveillance is reported in the NDA. The case is summarized below:

Table 5.74. Multiorgan Failure Associated with Rash

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
B0022235	Spont. Rep.	5	F	VPA Cefadroxil	12.5 mg	16D	No	SJS	fever, hypotension, hematuria, tachycardia	
B0022415	Spont. Rep.	4	M	VPA	50 mg	7D	No	Macular rash Fever		
A0036190	Spont. Rep.	8	F	VPA	25 mg (1.31 mg/kg)	16D	No	Rash Fever Facial oedema Thrombocytopenia		Medwatch 21-Mar-95
A0036191	Spont. Rep.	12	F	VPA	50 mg (1.57 mg/kg)	app. 2M	No	Rash Conjunctivitis SJS Elevated transaminase Elevated transaminase Elev. g-glutamyl transpep.		Medwatch 21-Mar-95 Follow-up 6-Oct-95
A0036196	Spont. Rep.	12	F	VPA	50 mg (0.53 mg/kg)	17D	No	SJS Elevated transaminase Elevated GGTP. Elevated transaminase Hallucination Drug interaction		Periodic Report 1-Apr-95 Follow-up 1-Jul-95
A0036211	Spont. Rep.	10	M	VPA PHT Tylenol Diphenhydramine	200 mg (6.58 mg/kg)	23D	No	SJS Allergic reaction Hepatitis Dehydration Tachycardia		Periodic Report 1-Jul-95

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
A0036311	Spont. Rep.	7	F	VPA	75 mg	3W	No	Bone marrow hypocellularity Rash Inc. liver function tests Hypersensitivity reaction EBV positive Lung infiltrates Fever Lymphadenopathy Decreased platelets Decreased WBC Decreased hemoglobin Increased LDH Increased SGOT Increased SPGT Dry oral mucous membranes Sore throat	Symptoms started 2 days after escalation to 25 mg tid.	Medwatch 29-Feb-96
B0022180	Spont. Rep.	12	F	VPA	100 mg	6D	No	Dizziness Nausea Macular rash Fever Malaise Jaundice		
B0022296	Spont. Rep.	6	F	Pivampicillin VPA	10 mg	app 1M	No	Drowsiness Fever Thrombocytopenia Maculopapular rash		

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
B0022303	Spont. Rep.	9	F	VPA	25 mg (1,09 mg/kg)	3D	No	DIC Multisystem failure Haemothorax Pneumonia Maculopapular rash Ulcerative stomatitis		
B0022463	Spont. Rep.	10	M	VPA Clobazam Amoxicillin Clavulanic acid Hydroxyzine Butamyrate	25 mg	26D	No	SJS Impaired liver function		Medwatch 16-Apr-96
B0022477	Spont. Rep.	8	M	VGB Clobazam Amoxicillin Ceftriaxone	50 mg	14D	Yes	SJS Cardiac failure Acute febrile episodes Acute renal failure Rash		
B0022485	Spont. Rep.	11	M	VPA	50 mg	2W	No	SJS Transaminase elevation Amylase elevation		
B0022556	Spont. Rep.	6	M	CBZ VPA	12.5 mg	14D	No	Allergic reaction Rash Vomitting Fever Pallor		

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
B0024382	Spont. Rep.	6	F	VPA DZP Pivampicillin	10 mg	40D	No	Fever Coagulation disorder Rash Face oedema Apathy Drug interaction		Medwatch 7-Jul-95
B0024754	Spont. Rep.	7	M	VPA	100 mg	9D	No	Erythema Neutropenia Thrombocytopenia Leucopenia Conjunctivitis		
B0022510	Spont. Rep.	6	M	VPA Clobazam VGB	12.5 mg	10D	No	Agranulocytosis Fever Fash Nausea Vomiting		
B0022333	Spont. Rep.	12	F	VPA	50 mg	14D	No	SJS	No adenopathy or increased LFTs.	
B0022227	Spont. Rep.	8	F	VPA	25 mg	23D	No	Fever Pharyngitis Erythematous rash Inflammation of oral mucosa Conjunctival reddening		
A0036195	Spont. Rep.	15	F	VPA Pseudephedrine Tylenol	50 mg (0.46 mg/kg)	20D	No	Allergic reaction Mucous membrane disorder Lymphadenopathy Maculopapular rash Abnormal liver function Eosinophilia		Periodic Report 1-Apr-95 Follow-up 1-Jul-95

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
A0036198	Spont. Rep.	14	M	PB	325 mg	app. 3W	No	Abnormal liver function Leukopenia Mucous membrane disorder Allergic reaction Rash Facial oedema		Periodic Report 1-Apr-95 Follow-up 1-Oct-95
A0036202	Spont. Rep.	13	F	VPA	50 mg	app. 3D	No	SJS Leukopenia Thrombocytopenia Anaemia Lymphadenopathy		Periodic Report 1-Apr-95 Follow-up 1-Oct-95
B0022222	Spont. Rep.	14	F	VPA MSM	100 mg	app. 4W	No	Lyell's syndrome	Increased trans-aminases, leukopenia.	
B0022260	Spont. Rep.	15	F	VPA DZP	25 mg (qod)	2W	No	Maculopapular rash Mucosal oedema Thrombocytopenia Fever		
B0024313	Spont. Rep.	13	F	VPA Lactulose	12.5 mg	13D	No	SJS DIC Thrombocytopenia Hyponatraemia Abnormal liver function tests		
B0022314	Spont. Rep.	13	F	VPA	40 mg	7W	No	SJS		
B0013801	Named Pat.	2	M	VPA CZP Budesonide Terbutaline	12.5 mg	15D	No	Macular Rash Exacerbation of Asthma Fever Tonsilitis Tympanitis Increased liver enzymes		

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
B0013821	Named Pat.	4	M	VPA Nitrazepam VGB Cefaclor	6.25 mg	11D	No	Skin erythema Pyrexia Stomatitis Ear infection Suspected septicemia		
B0014809	Named Pat.	2	M	VPA Cisipride Baclofen Chloral hydrate Magnapen	37.5 mg (2.1 mg/kg)	5D	No	Encephalopathy Encephalopathy SJS Pneumonia Status epilepticus Seizure		
B0013860	Named Pat.	5	F	VPA VGB CZP	5 mg (0.24 mg/kg)	15D	No	Fever Erythema Thrombocytopenia Sweet's syndrome		
B0013781	Named Pat.	7	F	VPA PRM Dexamethasone	100 mg	20D	No	Fever Rash Elevated LFTs		
B0013831	Named Pat.	7	F	VPA PRM Dexamethasone	100 mg	Unknown	No	Fever Rash Liver damage Leucocytosis Irritability Coagulopathy Hyperglycemia Acute liver failure		

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
B0013783	Named Pat.	13	F	VPA PB	100 mg	44D	No	SJS Balance problems Anorexia Hypoglycemia Thrombocytopenia Anaphylactic reaction Facial erythema Fever Rash		
B0013789	Named Pat.	15	M	VPA CZP	50 mg	22D	No	Maculopapular rash Fever Abnormal LFTs Mouth ulceration Vomiting Rigors		
B0013859	Named Pat.	14	F	VPA	25 mg	11D	No	Rash Edema of face Elevated transaminases Leukopenia Thrombocytopenia		
26-27-3	US26	4	M	CZP VPA	25 mg	10D	No	Maculopapular rash Fever Pancytopenia	Elevated LFTs on admission; LTG and VPA stopped.	

Table 5.74. Multiorgan Failure Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to Onset	Death?	Diagnosis	Comments	FDA Report
26-47-30	US26	6	F	VPA	6.25 mg	17D	No	Thrombocytopenia Rash Tongue edema Anorexia	Hx of this type of rash with VPA. Rash and tongue edema resolved when LTG stopped.	
26-2-1	US26	7	F	VPA	12.5 mg	12D	Yes	Fever Dehydration Rash Encephalitis ARDS DIC	Autopsy showed infection with hantavirus.	Safety update Feb 1994

Table 5.75. Multiorgan Failure Not Associated with Rash

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to onset	Death ?	Diagnosis	Comments	FDA report
B0022560	Spont. Rep.	2	M	VPA	Unknown	3M	Yes	Status Epilepticus DIC MOF Death		Medwatch 16-Apr-96
B0022411	Spont. Rep.	7	M	CBZ PHB	150 mg	6M	Yes	Increased prothrombin time Hepatomegaly Pneumonia Circulatory collapse Renal failure	Patient died; Disseminated Varicella may have contributed recent hx of status epilepticus.	Medwatch 16-Apr-96
B0022239	Spont. Rep.	7	F	DZP VGB	125 mg	10M	No	Abnormal liver function tests Prolonged convulsions Loss of consciousness		
B0026552	Spont. Rep.	6	M	VPA PHT LZP PB	25 mg	1M	Yes	Status epilepticus MOF Left ventricular hypertrophy Cardia arrest Coarctation of aorta Hypotension Comatose	Patient died	Medwatch 02-May-96
B0022365	Spont. Rep.	12	F	VPA	125 mg	2-3Y	No	MOF Coagulopathy Coma	Symptoms followed a prolonged convulsion.	
B0022527	Spont. Rep.	10	M	ESM VPA	Unknown	2Y	Yes	MOF	MOF and death followed status epilepticus.	Medwatch 16-Apr-96
B0022479	Spont. Rep.	14	M	CBZ PHT	Unknown	5M	Yes	Status epilepticus DIC Death		Medwatch 16-Apr-96

Table 5.75. Multiorgan Failure Not Associated with Rash (continued)

CSSS#	Source	Age	Sex	Concomitant Drugs	Dose at time	Days LTG to onset	Death ?	Diagnosis	Comments	FDA report
B0022143	Spont. Rep.	13	F	VGB VPA DZP PHT	Unknown	10M	Yes	MOF Epileptic attack DIC Hemorrhagic cerebral infarct Epidermal necrolysis	Patient died.	Medwatch 16-Apr-96
B0013897	Named Pt.	4	F	VPA PHT Clobazam	200 mg	870D	Yes	Status epilepticus Hepatotoxicity Rhabdomyolosis Fever Multi-organ failure Death		
B0013796	Named Pt.	14	M	VPA CZP	100 mg	60-90D	Yes	Status epilepticus Cardiac arrest DIC	Patient died. Pneumonia diagnosed.	Safety update Feb. 1994
26-51-39	US26	14M	M	VPA PHT PB	25 mg	60D	Yes	Status epilepticus Rhabdomyolosis Fever Coagulopathy Lactic acidosis Shock Death	MOF and death occurred after two prolonged episodes of status epilepticus.	

* A 7-year-old female (B13831) experienced fever, rash, and leucocytosis followed by acute liver failure and coagulopathy. Concomitant meds were VPA and primidone. Further details are not provided.

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Another case of liver failure in a child from post-marketing surveillance was reported in the MEDWATCH system in February, 1997 and is described below. It is not secondary to status epilepticus:

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* A 12 year-old male with polycystic kidney disease developed pallor, tachycardia, shortness of breath, and stomach pain 12 days after starting Lamictal and 2 days after a dose-escalation. He then developed a rash, fever, and joint pain. He was diagnosed with Scarlet Fever, treated with penicillin, and the rash improved. Lamictal was continued at a lower dose. He then developed hives, fever, vomiting, and swollen glands. Lamictal was stopped, but vomiting continued. Three days later he presented to the E.R. dehydrated, with a petechial rash and hepatomegaly. The next day his liver began to fail and he went into shock. He was diagnosed with a reaction to Lamictal and treated with steroids and FFP. Liver transplant was considered, but he improved and was discharged 10 days later. He subsequently lost all his hair, including eyebrows and eyelashes.

A death in a 7-year-old with status epilepticus, liver failure, and multi-organ failure is described above in Section 2.0 Deaths. While the investigator felt the multi-organ failure was possibly related to Lamictal, the case also seems consistent with a case of status epilepticus leading to multi-organ failure and death.

APPEARS THIS WAY ON ORIGINAL

7.0 Disseminated Intravascular Coagulation (DIC)

In my safety review for Lamictal for adult use, there is a section entitled "Unusual complications of status epilepticus leading to death." Two patients are described in that section. The first developed DIC 2 hours after an episode of status epilepticus was controlled. She died of massive bleeding. An autopsy revealed the presence of necrotizing enterocolitis. She had been on Lamictal for 9 months.

The second case was a 21 year-old female who developed DIC and multiple organ failure after status epilepticus. She had been of Lamictal for 6 months.

It was contended that these cases represented complications of status epilepticus and/or enterocolitis rather than a serious reaction to Lamictal itself.

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In the January 17, 1997 safety update (page 18;volume 1), the sponsor cites a reference[5] which describes 2 pediatric cases of multiple organ failure with DIC in Canada. Both patients presented with rashes within 2 weeks of starting Lamictal with VPA. The sponsor states that these cases are consistent with the knowledge of the AED hypersensitivity syndrome seen with Lamictal.

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ON ORIGINAL

On the contrary, these cases are not consistent with our knowledge of the AED hypersensitivity syndrome seen with Lamictal. Outside of these 2 cases in children and one previously published case in an adult, all other cases of DIC with Lamictal have, to my knowledge, appeared to be secondary phenomena in cases of multi-organ failure after sepsis or status epilepticus. A review of Sponsor's Table 5.74 reveals 5 cases of DIC or "coagulopathy": B22303, B24382, B24313, B13831, and Pt.26-2-1. A case can be made for these 5 patients that the DIC and/or coagulopathy were secondary to the severity of other organ involvement (Hanta virus, SJS, etc). I am not aware of any cases of DIC occurring as an isolated AE with Lamictal. To my knowledge, DIC is not part of the *usual* picture of HSS seen with Lamictal or any other drug and I believe it is for this reason that the authors published their abstract.

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ON ORIGINAL

The occurrence of DIC in these cases only blurs the distinction between the two categories of multi-system failure known to occur with Lamictal (see Section 6.0 above). The occurrence of DIC in fatal cases of status epilepticus seen with Lamictal has previously been attributed to the status epilepticus alone; if DIC is now being linked to Lamictal, it suggests that these fatalities (even the concurrent status epilepticus) might be linked to a Lamictal reaction. My review of the deaths with associated DIC still supports the notion that DIC was secondary to status epilepticus or sepsis in those cases. Care must be exercised in the future surveillance of deaths with Lamictal to determine that the pattern of deaths is not changing.

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[5]Chattergoon, McGuigan, Koren, Hwang, and Ito. Multiorgan dysfunction and DIC in two children following lamotrigine and valproic acid. Clin and Investig Med 1996; 19 (4 suppl):S12.

8.0 Laboratory Assessments

The sponsor reports no significant problems with hematology, chemistry, or urinalysis values during the Lamictal CD NDA studies. Likewise, no significant EKG abnormalities emerged during drug treatment.

In post-marketing surveillance, there clearly are a number of patients with low or borderline platelet counts and WBC counts. These appear to occur along with other AEs, to include rash, and do not reach. alarming levels in the absence of other serious events, such as SJS/TEN (see Sponsor's Table 5.74).

9.0 Other Regulatory Actions

Lamictal Tablets were approved in the US on 27 December 1994 for the treatment of partial seizures in adults. Lamictal is not currently approved in any country for treatment of Lennox-Gastaut Syndrome. It is currently approved in 14 countries for treatment of pediatric patients (ages 2-12 years) with epilepsy, including the UK and Ireland.

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Conclusions:

The risk estimates of SJS/TEN are as high as 1/50-1/300 in pediatric populations. There are 7 independent sources for these estimates:

1. Published experience in Nova Scotia by Dooley, et al.
2. Published experience by Arnold, et al.
3. UK 123
4. JP 01
5. JP 02
6. US 40
7. PEM pediatric data

Supportive information comes from the consult by Dr. Harold Davis in HFD-730.

There is no firm evidence that lower starting doses and slower dose escalation will reduce this risk. While such a strategy has been shown to reduce the risk of minor rash with Lamictal, SJS/TEN may have a different pathophysiology than minor rash, making such strategies futile.

The sponsor may be able to make the case that concomitant VPA increases the risk of SJS/TEN and, further, that the greater use of VPA in pediatric populations may explain the greater risk of SJS/TEN in children. However, the sponsor has not made this point convincingly yet. (And cases of SJS/TEN are occurring with Lamictal in the absence of VPA.) If the point were made, it might warrant contraindication of concomitant VPA and Lamictal usage. (A dilemma would then present itself in that the single

study submitted to support efficacy in pediatric populations includes a large percentage of patients, 68%, treated with concomitant VPA.)

The sponsor must make every effort to unravel these issues quickly given the databases available. The PEM data might be broken down by age-group and concomitant VPA usage to clarify the relative role of age and VPA. If VPA does not elevate the risk of SJS/TEN, then Lamictal might be contraindicated in children, given the risk estimates as high as 1/50. If VPA does elevate the risk of SJS/TEN, then Lamictal might be contraindicated with concomitant VPA in both adults and children.

Meanwhile, in the absence of this information, the fact remains that in the single pivotal trial submitted to support the use of Lamictal in children, 1/40 children experienced a potentially life-threatening rash.

/S/

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John Feeney, M.D.
Medical Reviewer
March 7, 1997

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

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