

Type IV hypersensitivity reaction

Investigations

Alanine Aminotransferase Increased
Lipase increased
Aspartate Aminotransferase Increased
Eosinophil Count Increased
Granulocyte Count Decreased
Hepatic Enzyme Abnormal
Hepatic Enzyme Increased
Liver Function Test Abnormal
Neutrophil Count Decreased
Platelet Count Decreased
Lymphocyte count increased
White blood cell count increased
Monocyte count increased
Basophil count increased
White blood cell morphology abnormal
Biopsy liver abnormal
Biopsy kidney abnormal
Biopsy lung abnormal
Immunology test abnormal
Biopsy skin abnormal
Urinary casts

Musculoskeletal and connective tissue disorders

Arthritis
Myositis
Polyarthritis
Joint swelling
Joint warmth
Arthralgia
Arthropathy

Neoplasm, benign, malignant and unspecified

Pseudolymphoma

Renal and urinary disorders

Nephropathy toxic
Nephritis
Nephropathy toxic
Renal failure
Proteinuria
Hematuria
Oliguria
Nephrotic syndrome
Nephritis allergic
Nephritic syndrome
Nephritis interstitial
Eosinophilic cystitis_a

Respiratory, thoracic and mediastinal disorders

Interstitial lung disease

Pneumonitis

Alveolitis

Alveolitis allergic

Eosinophilic bronchitis^a

Eosinophilic pneumonia^a

Skin and subcutaneous tissue disorders

Eosinophilic cellulitis^a

Laboratory value criteria

Eosinophils % $\geq 10\%$

Eosinophils absolute $\geq 0.5\text{G/L}$

Neutrophils absolute $< 1.5\text{G/L}$

Platelets $\leq 100\text{G/L}$

ALT $\geq 2\text{xULN}$

AST $\geq 2\text{xULN}$

ALT=alanine aminotransferase; AST=aspartate aminotransferase; iv=intravenous;
LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities;
SOC=system organ class; ULN=upper limit of normal

a Preferred term is included in the MedDRA Version 11.0 SOC of 'Blood and lymphatic disorders' in the document provided by the Division. For this table, however, the preferred term is listed under the Primary SOC for MedDRA Version 9.1 (which is utilized in the original submission and this response).

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 4. Adverse events suggestive of fever, rash, or lymphadenopathy (Group B) in subjects treated with LCM as submitted on (08/14/08 submission)

MedDRA® SOC/Preferred term

Blood and lymphatic system disorders

Lymphadenitis

Lymphadenopathy

Lymphadenopathy Mediastinal

General disorders and administration site conditions

Pyrexia

Immune system disorders

Drug rash with eosinophilia and systemic symptoms

Skin and subcutaneous tissue disorders

Dermatitis Allergic

Rash

Rash Erythematous

Rash Generalised

Rash Macular

Rash Macular-Papular

Rash Morbilliform

Rash Papular

Rash Pruritic

Rash Psoriaform

Drug Eruption

Urticaria

Toxic skin eruption

Exfoliative rash

Skin exfoliation

Rash vesicular

iv=intravenous; LCM=lacosamide; MedDRA®=Medical Dictionary for Regulatory Activities; SOC=system organ class

a Preferred term is included in the MedDRA Version 11.0 SOC of 'Skin and subcutaneous tissue disorders' in the document provided by the Division. For this table, however, the preferred term is listed under the Primary SOC for MedDRA Version 9.1 (which is utilized in the original submission and this response).

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 5. Summary table of potential cases of multiorgan hypersensitivity identified in lacosamide trials, using the FDA suggested approach. Cases added in 8/08 are bolded.

Subjects with new or revised narratives based on identification of a potential case of multi-organ hypersensitivity using the Division-directed algorithm

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification ^a : AE or lab value criteria	AE outcome
Phase 1				
588008053	588008053	Revised	Group A: Joint swelling	Ongoing
			Group B: Rash pruritic (18 Oct 2000),	Recovered/resolved
			Rash pruritic (19 Oct 2000),	Recovered/resolved
			Rash pruritic (19 Oct 2000),	Recovered/resolved
			Rash pruritic (20 Oct 2000)	Recovered/resolved
640082076 ^{b,c}	640082076	Revised	Group A: Hypersensitivity	Recovered/resolved
			Group B: Skin exfoliation	Recovered/resolved
641080204	641080204	New	Group A: Arthralgia	Recovered/resolved
			Group B: Lymphadenopathy	Recovered/resolved
641080501	641080501	New	Group A: Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Lymphadenopathy	Recovered/resolved
836000010	836000010	New	Group A: ALT increased	Resolved
			Group B: Rash	Resolved
Partial-onset seizures				
607001454	607001454	Revised	Group A: Neutrophils absolute <1.5G/L	NA (lab value)
			Group B: Rash erythematous	Not yet completely resolved
615010052	598003003	New	Group A: Eosinophils absolute ≥0.5G/L	NA (lab value)
			Group B: Dermatitis allergic	Recovered/resolved
615011028	667012406	New	Group A: Haematuria	Recovered/resolved
			Group B: Pyrexia	Recovered/resolved

Appendix 5. Cont.

Narrative subject number	CTD integrated database subject number	New or revised narrative	Basis of identification ^a : AE or lab value criteria	AE outcome
667010102	667010102	Revised	Group A: Arthralgia	Recovered/resolved
			Group B: Rash (05 Mar 2003), Rash (09 Apr 2003)	Recovered/resolved Recovered/resolved
667011005 ^c	667011005	Revised	Group A: Hypersensitivity	Recovered/resolved
			Group B: Rash	Recovered/resolved
667011801	667011801	Revised	Group A: Eosinophil count increased, Eosinophil count increased, Eosinophils % $\geq 10\%$, Eosinophils absolute $\geq 0.5G/L$	Recovered/resolved Recovered/resolved NA (lab value) NA (lab value)
			Group B: Lymphadenopathy	Recovered/resolved
667011814	667011814	Revised	Group A: Joint swelling	Recovered/resolved
			Group B: Rash	Recovered/resolved
667013511	667013511	Revised	Group A: Eosinophils % $\geq 10\%$, Eosinophils absolute $\geq 0.5G/L$, Neutrophils absolute $< 1.5G/L$	NA (lab value) NA (lab value) NA (lab value)
			Group B: Rash	Recovered/resolved
755100804 ^d	755100804	Revised	Group A: Leukopenia	Recovered/resolved
			Group B: Rash	Recovered/resolved
755124101	755124101	Revised	Group A: Eosinophils % $\geq 10\%$, Neutrophils absolute $< 1.5G/L$	NA (lab value) NA (lab value)
			Group B: Rash	Recovered/resolved
756012005	754012005	Revised	Group A: Neutropenia, Neutrophils absolute $< 1.5G/L$	Recovered/resolved NA (lab value)
			Group B: Rash	Recovered/resolved

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