

Spontaneously Reported TESAEs During All Short-Term Studies (US and European)

Below is a table of TESAEs in the acamprosate group from short-term Group 1 studies that collected AEs spontaneously and were reported by at least one acamprosate randomized patient. Shaded SAEs in the table below are those that were reported by more than one patient. None of the overdose cases died; and only one overdose (UKMAS – 570) involved an unstated amount of acamprosate along with ethanol.

Although the source table for the table below lists 1 death in the placebo group, there are 3 patients among the death narratives for patients who died in the UKMAS study: 1 on acamprosate 1998 mg/day (UKMAS – 297) who experienced *accidental injury/ subdural hematoma* after falling while intoxicated and also experienced multiple grand mal seizures; and 2 on placebo (UKMAS - 227) *accidental fall* with fatal *intracranial hemorrhage* and (UKMAS - 484) liver failure. It is not clear why all 3 patients were not included in the source table.

In comparison to the table for the US study by itself, this table shows the emergence of *anxiety, accidental injury, overdose, and suicide attempt* as SAEs in more than one patient; and *paranoid reaction, cerebrovascular disorder, encephalopathy, subdural hematoma, thirst, diarrhea, gastroenteritis, pancreatitis, syncope, angina pectoris, deep thrombophlebitis, MI, breast neoplasm, polyuria, and unintended pregnancy* emerge as events in one patient each. *Depression and GI bleed* increased by 1 and 2 patients, respectively.

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TESAEs in the ACAMP Group from Short-Term Studies with Spontaneously Reported AEs - US 96.1, UKMAS, ADISA (Shaded rows contain more than 1 acamprosate treated patient)	ACAMP 1998/2000 mg/day	ACAMP Pooled (Includes 3000 mg dose from US study)	Placebo
Number of patients	694	777	700
Number of patients with a serious adverse event	34 (5%)	36 (5%)	21 (3%)
Depression	3 (<1%)	3 (<1%)	1 (<1%)
Convulsion	1 (<1%)	1 (<1%)	1 (<1%)
Paranoid reaction	1 (<1%)	1 (<1%)	1 (<1%)
Anxiety	2 (<1%)	2 (<1%)	0
Cerebrovascular disorder	1 (<1%)	1 (<1%)	0
Encephalopathy	1 (<1%)	1 (<1%)	0
Subdural hematoma	1 (<1%)	1 (<1%)	0
Agitation	0	1 (<1%)	0
Accidental injury	4 (<1%)	4 (<1%)	4 (<1%)
Overdose	5 (<1%)	5 (<1%)	2 (<1%)
Abdominal pain	1 (<1%)	1 (<1%)	1 (<1%)
Suicide attempt	3 (<1%)	3 (<1%)	0
Back pain	1 (<1%)	1 (<1%)	0
Cellulitis	1 (<1%)	1 (<1%)	0
Infection	1 (<1%)	1 (<1%)	0
Infection parasitic	1 (<1%)	1 (<1%)	0
Hypokalemia	1 (<1%)	1 (<1%)	0
Thirst	1 (<1%)	1 (<1%)	0
Diarrhea	1 (<1%)	1 (<1%)	1 (<1%)
Gastrointestinal hemorrhage	3 (<1%)	3 (<1%)	0
Gastroenteritis	1 (<1%)	1 (<1%)	0
Pancreatitis	1 (<1%)	1 (<1%)	0
Syncope	1 (<1%)	1 (<1%)	1 (<1%)
Angina pectoris	1 (<1%)	1 (<1%)	0
Deep thrombophlebitis	1 (<1%)	1 (<1%)	0
MI	1 (<1%)	1 (<1%)	0
Breast carcinoma	1 (<1%)	1 (<1%)	0
Breast neoplasm	1 (<1%)	1 (<1%)	0
Polyuria	1 (<1%)	1 (<1%)	0
Unintended pregnancy	1 (<1%)	1 (<1%)	0
Asthma	0	1 (<1%)	0

Source: In-Text Table 8.8.7.1.1.1 from Post-Text Table 8.8.8.0.0 Vol 68 p 185

Spontaneously Reported TESAEs During Long-Term European Studies

Below is a table displaying SAEs that occurred in the acamprosate group from long-term studies reporting AEs spontaneously. SAEs occurring in more than one acamprosate treated patient included *accidental injury*, *suicide attempt* and *MI*. The number of patients experiencing these events is similar between the acamprosate group compared to placebo group except *MI* that had 3 in the acamprosate group and none in the placebo group.

TESAEs in the ACAMP Group from Long-Term Studies with Spontaneously Reported AEs – PRAMA, Paille (Shaded rows contain more than 1 acamprosate treated patient)	ACAMP 1998/2000 mg	Pooled ACAMP (Includes 1332 mg dose from PRAMA and Paille)	Placebo
Number of Patients	285	497	313
Number of Patients with a SAE	14 (5%)	23 (5%)	15 (5%)
Accidental Injury	1 (<1%)	4 (<1%)	4 (1%)
Suicide Attempt	2 (<1%)	2 (<1%)	1 (<1%)
Neuroleptic Malignant Syndrome	0	1 (<1%)	0
Depression	0	1 (<1%)	2 (<1%)
Convulsion	1 (<1%)	1 (<1%)	0
Hematemesis	0	1 (<1%)	1 (<1%)
GI Hemorrhage	1 (<1%)	1 (<1%)	0
MI	2 (<1%)	3 (<1%)	0
Mesenteric Occlusion	1 (<1%)	1 (<1%)	0
Syncope	1 (<1%)	1 (<1%)	0
Prostatic Disorder	0	1 (<1%)	0
Kidney Failure	1 (<1%)	1 (<1%)	0
Unintended Pregnancy	1 (<1%)	1 (<1%)	0
Urogenital Disorder	1 (<1%)	1 (<1%)	0
Hypoglycemia	0	1 (<1%)	0
Arthrosis	1 (<1%)	1 (<1%)	0
Joint Disorder	1 (<1%)	1 (<1%)	0
Source: Post-Text Table 8.8.8.2.0			

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Below is a combined table of TESAEs from all (short-term and long-term) Group 1 placebo-controlled studies that collected AEs by spontaneous reporting only. While the number of patients within each cell is small there are notable differences between placebo and pooled acamprosate groups for *suicide attempt, GI hemorrhage, and MI*.

Overall Incidence of Spontaneously Reported Treatment-Emergent Serious Adverse Events For TESAEs that Occurred in 1 or more Acamprosate Treated Patients – Short-Term and Long-Term Placebo-Controlled Group 1 Studies (US 96.1, UKMAS, ADISA, PRAMA, Paille) (Shaded rows contain more than 1acamprosate treated patient)					
Number of Patients	1013	212	979	83	1274
Number of Patients with a SAE	36 (4%)	9 (4%)	48 (5%)	2 (2%)	59 (5%)
Preferred Term	Placebo	ACAMP 1332 mg	ACAMP 1998/2000 mg	ACAMP 3000 mg	ACAMP Pooled
Accidental Injury	8 (<1%)	3 (1%)	5 (<1%)	0	8 (<1%)
Suicide Attempt	1 (<1%)	0	5 (<1%)	0	5 (<1%)
Neuroleptic Malignant Syndrome	0	1 (<1%)	0	0	1 (<1%)
Depression	3 (<1%)	1 (<1%)	3 (<1%)	0	4 (<1%)
Convulsion	1 (<1%)	0	2 (<1%)	0	2 (<1%)
Hematemesis	3 (<1%)	1 (<1%)	0	0	1 (<1%)
GI Hemorrhage	0	0	4 (<1%)	0	4 (<1%)
MI	0	1 (<1%)	3 (<1%)	0	4 (<1%)
Mesenteric Occlusion	0	0	1 (<1%)	0	1 (<1%)
Syncope	1 (<1%)	0	2 (<1%)	0	2 (<1%)
Prostatic Disorder	0	1 (<1%)	0	0	1 (<1%)
Kidney Failure	0	0	1 (<1%)	0	1 (<1%)
Unintended Pregnancy	0	0	2 (<1%)	0	2 (<1%)
Urogenital Disorder	0	0	1 (<1%)	0	1 (<1%)
Hypoglycemia	0	1 (<1%)	0	0	1 (<1%)
Arthrosis	0	0	1 (<1%)	0	1 (<1%)
Joint Disorder	0	0	1 (<1%)	0	1 (<1%)
Overdose	2 (<1%)	0	5 (<1%)	0	5 (<1%)
Abdominal Pain	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Back Pain	0	0	1 (<1%)	0	1 (<1%)
Cellulitis	0	0	1 (<1%)	0	1 (<1%)
Infection	0	0	1 (<1%)	0	1 (<1%)
Infection Parasitic	0	0	1 (<1%)	0	1 (<1%)
Paranoid Reaction	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Anxiety	0	0	2 (<1%)	0	2 (<1%)
Cerebrovascular Disorder	0	0	1 (<1%)	0	1 (<1%)
Encephalopathy	0	0	1 (<1%)	0	1 (<1%)
Subdural Hematoma	0	0	1 (<1%)	0	1 (<1%)
Agitation	0	0	0	1 (1%)	1 (<1%)
Diarrhea	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Gastroenteritis	0	0	1 (<1%)	0	1 (<1%)
Pancreatitis	0	0	1 (<1%)	0	1 (<1%)
Angina Pectoris	0	0	1 (<1%)	0	1 (<1%)
Deep Thrombophlebitis	0	0	1 (<1%)	0	1 (<1%)
Breast Carcinoma	0	0	1 (<1%)	0	1 (<1%)
Breast Neoplasm	0	0	1 (<1%)	0	1 (<1%)
Polyuria	0	0	1 (<1%)	0	1 (<1%)
Hypokalemia	0	0	1 (<1%)	0	1 (<1%)
Thirst	0	0	1 (<1%)	0	1 (<1%)
Asthma	0	0	0	1 (1%)	1 (1%)

Source: Post-Text Tables 8.8.8.0.0; 8.8.8.2.0 Vol. 68 p 185, 204

Narratives Provided for TESAEs Across the NDA

Narratives in the ISS are provided across the NDA for 145 Group 1 patients who experienced one or more SAE. Of the 145 narratives 124 described non-death SAEs. Review of the narratives for the patients who were randomized to acamprosate and experienced at least 1 SAE shows no clear attribution to acamprosate to the SAE. However, the majority of narratives generally contained little more than patient ID, gender, age, SAE, duration of treatment, investigator's attribution to treatment, and discontinuation status; diagnostic work-up and laboratory values were seldom included. There were no SAE narratives for patients randomized to acamprosate in the Group 1 studies suggestive of agranulocytosis, anaphylaxis, aplastic anemia, rhabdomyolysis, or Stevens Johnson Syndrome. Numbers of notable SAEs narratives are presented in the table below.

Numbers of TESAEs with an Excess in the Acamprosate Group		
Event	Acamprosate Pooled	Placebo
Depression	4	3
Suicidal Ideation (separate from depression)	3	0
Suicide Attempt (not overdose)	5	0
Overdose (various substances with or without acamprosate)	5	2
MI	4	2
Angina	2	0
CHF (due to cardiomyopathy)	1	0
Convulsions/Seizures	4	3
Gastrointestinal Bleed	4	2
Pancreatitis	1	0
Asthma Attack	1	0
Rash (hospitalization needed)	1	0
Renal Failure	1	0
Psychiatric Reactions	7	3

Withdrawals Due to Adverse Events

The sponsor provides tables summarizing reasons for patient withdrawal due to adverse events for Group 1 studies. In the ISS in-text tables are provided only for the US trial alone, and combined with short-term European trials. No in-text tables are provided for short-term European trials alone or for the long-term European trials. The table for short-term placebo-controlled trials is reproduced below. According to the sponsor's analysis, the most common AE reasons for withdrawal in the acamprosate treatment groups in short-term trials were: depression (2%), headache (1%), diarrhea (2%), nausea (1%), vomiting (<1%), and alcohol intolerance (1%). From long-term trials the sponsor sites most common AE reason for withdrawal was: diarrhea - pooled acamprosate 7 (1%) vs. placebo 2 (<1%).

As with other AE listings for this NDA it is difficult to verify the incidence of reasons for withdrawal because the coding of verbatim terms to preferred COSTART terms appears inconsistent. By my count the sponsor also provides 292 narratives or reference to other narratives (deaths and serious AEs) for premature withdrawal due to an AE; among these 292 citations are 10 references to deaths and 81 references to non-death serious AEs, totaling 201 non-serious AEs narratives for premature withdrawal. It is not clear why narratives for the other 12 Group 1 deaths were not referenced in the listing of narratives for premature withdrawals. Further, counting the premature withdrawals for Group 1 studies yields a total of 305 withdrawals due to an AE (180 on acamprosate; 125 on placebo) yet only 292 narratives are provided. The 305 cases were tabulated from the incidence tables for premature withdrawals due to an AE in the studies collecting AEs spontaneously and from the listing of withdrawals for studies collecting AEs using a list to collect AEs; no incidence tables for studies collecting AEs using an AE list could be found in the NDA. Considering these inconsistencies and the inability to verify these numbers of cases using the electronic datasets, no analyses were conducted by the Agency.

Spontaneously Reported Adverse Events Leading to Premature Discontinuation Reported for More Than One Patient in Any Treatment Group in the Controlled Short-Term Studies US 96.1, UKMAS, and ADISA Safety Population

Body System/Preferred Term	Statistic	ACAMP 1998/2000 mg/day	ACAMP Pooled	Placebo
Number of patients	N	694	777	700
Number of patients with an adverse event leading to withdrawal	n (%)	76 (11%)	84 (11%)	48 (7%)
Nervous system	n (%)	28 (4%)	31 (4%)	23 (3%)
Depression	n (%)	11 (2%)	12 (2%)	6 (<1%)
Withdrawal syndrome	n (%)	5 (<1%)	5 (<1%)	2 (<1%)
Hallucinations	n (%)	1 (<1%)	1 (<1%)	2 (<1%)
Hypertension	n (%)	1 (<1%)	1 (<1%)	2 (<1%)
Grand mal convulsion	n (%)	0	0	2 (<1%)
Paresthesia	n (%)	0	0	2 (<1%)
Anxiety	n (%)	3 (<1%)	3 (<1%)	1 (<1%)
Drug dependence	n (%)	2 (<1%)	2 (<1%)	1 (<1%)
Somnolence	n (%)	3 (<1%)	3 (<1%)	0
Body as a Whole	n (%)	23 (3%)	25 (3%)	15 (2%)
Abdominal pain	n (%)	5 (<1%)	6 (<1%)	7 (1%)
Overdose	n (%)	4 (<1%)	4 (<1%)	2 (<1%)
Accidental injury	n (%)	2 (<1%)	2 (<1%)	2 (<1%)
Pain	n (%)	2 (<1%)	2 (<1%)	1 (<1%)
Headache	n (%)	7 (1%)	8 (1%)	0
Suicide attempt	n (%)	3 (<1%)	3 (<1%)	0
Digestive system	n (%)	22 (3%)	27 (3%)	14 (2%)
Diarrhea	n (%)	14 (2%)	17 (2%)	5 (<1%)
Nausea	n (%)	8 (1%)	8 (1%)	2 (<1%)
Melena	n (%)	0	0	2 (<1%)
Vomiting	n (%)	5 (<1%)	6 (<1%)	1 (<1%)
Flatulence	n (%)	2 (<1%)	2 (<1%)	1 (<1%)
Gastrointestinal hemorrhage	n (%)	2 (<1%)	2 (<1%)	0
Metabolic and nutritional disorders	n (%)	7 (1)	9 (1%)	4 (<1%)
Alcohol intolerance	n (%)	6 (<1%)	8 (1%)	4 (<1%)
Cardiovascular system	n (%)	6 (<1%)	6 (<1%)	3 (<1%)
Syncope	n (%)	2 (<1%)	2 (<1%)	1 (<1%)
Urogenital	n (%)	6 (<1%)	7 (<1%)	1 (<1%)
Unintended pregnancy	n (%)	2 (<1%)	2 (<1%)	0
Impotence	n (%)	1 (<1%)	2 (<1%)	0
Skin and appendages	n (%)	4 (<1%)	4 (<1%)	1 (<1%)
Rash	n (%)	2 (<1%)	2 (<1%)	1 (<1%)
Pruritus	n (%)	2 (<1%)	2 (<1%)	0

Data Source: Post-Text Table 8.8.7.0.0; In-Text Table 8.8.6.1.1:1

Note: Adverse events included in this table led to study drug discontinuation and were considered either a primary or secondary reason for discontinuation.

Note: Patients are counted only once within each body system and preferred term.

Note: Adverse events were coded using the COSTART dictionary.

Note: Some patients who withdrew due to adverse events had reason for discontinuation other than "Adverse Event" (often treatment failure or patient refusal).

Note: Data for the acamprostate 3000 mg/day group (N=83) are not included in this In-Text Table, but can be found in the table being referenced.

Common Treatment Emergent Adverse Events (TEAEs) in Group 1 Studies

AEs were collected from spontaneous reports in 5 Group 1 studies, US96.1, UKMAS, ADISA, PRAMA, and Paille while all other Group 1 studies collected AEs using a 43-item questionnaire. For this reason, the sponsor analyzed AEs by these two sub-groups of studies. Additionally, the US trial was analyzed separately. The integrated database for the Group 1 studies shows that a much broader spectrum of AE terms were captured in the database for spontaneously collected AEs compared to the database for AEs collected using the list of 43-items. There are 344 preferred terms for spontaneous collection compared 40 preferred terms for list collection. The electronic database does not integrate them into one database but rather has two separate files, one for spontaneously reported AEs and one for list reported AEs. The sponsor proposes that in the draft labeling to include adverse event rates only from the database of spontaneously reported adverse events.

Verbatim AE terms were coded using the COSTART dictionary. My review of the coding of verbatim terms to preferred COSTART terms shows that the coding may not be appropriate or consistent and raises concern over the reliability of the database. The following are examples:

- 1) hypertensive terms have been subsumed in *hypertension* and then in the nervous system instead of cardiovascular system;
- 2) *alcohol intoxication* has been subsumed in *stupor* and in *alcohol intolerance* and should be subsumed in only one preferred term;
- 3) *alcohol intolerance* has been subsumed in the metabolic and nutritional disorders body system and should be subsumed in body as a whole;
- 4) *drug dependence*, *stupor*, and *withdrawal syndrome* have been subsumed in the nervous system and should be subsumed in body as a whole;
- 5) specific joint pain terms are subsumed in *pain* and then in body as a whole and should be subsumed in arthralgia;
- 6) *suicide* verbatim terms are not consistently coded – for example, in the SS_AEs database subject 32 (study 4) has a verbatim term of suicide and is coded to the terms death and suicide attempt; but subject 236 (study10) has a verbatim term of suicide but is coded only to suicide attempt and not to death.. A similar comparison can be made for subject 106 (study 3) and subject 29 (study 3).
- 7) Audit of the electronic database for spontaneously reported AEs shows that some patients who were hospitalized for various reasons were not flagged as serious AEs but were flagged as TEAEs. The following are examples:

Patient – Study Number – Term

37	11	Colitis
184	15	MI
294	15	Accidental Injury (foot fracture – no narrative)
360	15	GI hemorrhage (no narrative)
383	15	Neurosis (no narrative)
532	15	Colitis (no narrative)

Below is a table condensed from the sponsor's post-text table for study, US 96.1, conducted in the U.S. and collected all AEs spontaneously reported. Although AEs were spontaneously collected, this table should be interpreted recognizing the overall small numbers of patients randomized. The table below displays those AEs reported $\geq 2\%$ in either acamprosate dose group and approximately 2 fold greater in either acamprosate group compared to the placebo group. Notable AEs occurring at approximately 10% or greater in either acamprosate dose group are *diarrhea*, *flatulance*, and *hyperglycemia*; all three appear to be related to acamprosate treatment but *hyperglycemia* occurred at 10% only in the 3000 mg dose group. Shaded AEs are those that occurred at a 2 fold or greater incidence in the 3000 mg acamprosate group compared to the 1998/2000 mg dose group which may suggest a dose response; they include: fever, dyspepsia, anxiety, contact dermatitis, hyperglycemia, hyperuricemia, and impotence. *Eosinophilia* and *impotence* occurred only the acamprosate groups but not in the placebo group and also may represent an acamprosate effect, although these AEs occurred in only a few patients.

AEs that occurred at less than 2% in either acamprosate dose group are not in the table below; those that occurred in at least 2 acamprosate patients but not in the placebo group include: *neoplasm, libido increased, neuropathy, vaginitis, lymphocytosis, and hemorrhage.*

Spontaneously Reported TEAEs ≥ 2% in ACAMP Patients And Approximately 2 Fold Greater in Either Dose of ACAMP Patients Than Placebo Patients – Controlled Short-Term Study US 96.1 (Shaded TEAEs occurred at 3000 mg at 2 fold or greater than 1998/2000 mg)			
Preferred Term	ACAMP 1998/2000 mg	ACAMP 3000 mg	Placebo
Number of Patients	258	83	260
Number of Patients with an Adverse Event	221 (86%)	73 (88%)	218 (84%)
Back Pain	12 (5%)	2 (2%)	9 (3%)
Fever	2 (<1%)	3 (4%)	3 (1%)
Lab Test Abnormal	6 (2%)	0	1 (<1%)
Diarrhea	86 (33%)	33 (40%)	48 (18%)
Flatulence	22 (9%)	4 (5%)	8 (3%)
Dyspepsia	10 (4%)	7 (8%)	6 (2%)
Increased Appetite	4 (2%)	0	3 (1%)
Vomiting	10 (4%)	4 (5%)	2 (<1%)
Gastrointestinal Disorder	4 (2%)	2 (2%)	1 (<1%)
Anxiety	7 (3%)	5 (6%)	8 (3%)
Libido Decreased	7 (3%)	4 (5%)	8 (3%)
Hypertension	12 (5%)	2 (2%)	5 (2%)
Agitation	0	2 (2%)	2 (<1%)
Hypertonia	7 (3%)	3 (4%)	1 (<1%)
Sweating	4 (2%)	2 (2%)	3 (1%)
Dry Skin	4 (2%)	2 (2%)	2 (<1%)
Contact Dermatitis	0	2 (2%)	2 (<1%)
Hyperglycemia	10 (4%)	8 (10%)	12 (5%)
Hyperuricemia	3 (1%)	3 (4%)	3 (1%)
Menstrual Disorder	4 (2%)	0	3 (1%)
Urinary Frequency	4 (2%)	0	1 (<1%)
Impotence	2 (<1%)	2 (2%)	0
Erythrocytes Abnormal	8 (3%)	4 (5%)	8 (3%)
Eosinophilia	5 (2%)	1 (1%)	0

Source: Post-Text Table 8.8.6.0.1

Below is a table condensed from the sponsor's post-text table for controlled short-term European studies, UKMAS and ADISA, that collected AEs spontaneously reported. The table below displays those AEs reported $\geq 2\%$ in the acamprosate dose group and approximately 2 fold greater in the acamprosate group compared to the placebo group. The only notable AE occurring at greater than 10% in the acamprosate group is *diarrhea*.

AEs that occurred at less than 2% in the acamprosate dose group are not in the table below; those that occurred in at least 2 acamprosate patients but not in the placebo group include: *suicide attempt, allergic reaction, apathy, gastrointestinal hemorrhage, maculopapular rash, unintended pregnancy, hypotension, tachycardia, and blepharitis*.

Spontaneously Reported TEAEs $\geq 2\%$ in ACAMP Patients And Approximately 2 Fold Greater in ACAMP Patients Than Placebo Patients (Controlled Short-Term European Studies UKMAS and ADISA)		
(From Short-Term EUROPEAN Studies)		
Preferred Term	ACAMP 1998/2000 mg	Placebo
Number of Patients	436	440
Number of Patients with an Adverse Event	286 (66%)	274 (62%)
Malaise	7 (2%)	1 (<1%)
Diarrhea	92 (21%)	57 (13%)
Flatulence	26 (6%)	12 (3%)
Arthralgia	11 (3%)	6 (1%)

Source: Post-Text Table 8.8.6.0.2

Below is a table condensed from the sponsor's post-text table for controlled European long-term studies, PRAMA and Paille, that collected AEs spontaneously reported. The table below displays those AEs reported $\geq 2\%$ in either acamprosate dose group and approximately 2 fold greater in either acamprosate group compared to the placebo group. The only notable AE occurring at greater than 10% in either acamprosate dose group is *diarrhea* and the increase from 6% in placebo to 9% in the 1332 mg dose and to 12% in 1998/2000 mg dose may show a trend toward a dose effect. Shaded AEs are those that occurred at a 2 fold greater incidence in the 1988/2000 mg acamprosate group compared to the 1332 mg dose group which may suggest a dose response; they include: *flu syndrome, flatulence, and weight gain*. *Flatulence* occurred only the acamprosate groups but not in the placebo group which may represent an acamprosate effect.

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AEs that occurred at less than 2% in either acamprosate dose group are not in the table below; those that occurred in at least 2 acamprosate patients but not in the placebo group include: *malaise, hostility, abnormal thinking, amnesia, hepatitis, esophageal hemorrhage, peripheral edema, thirst, hyperuracemia, maculopapular rash, arrhythmia, migraine, myocardial infarction, arteriosclerosis, varicose vein, kidney pain, arthrosis, and joint disorder.*

Spontaneously Reported TEAEs \geq 2% in ACAMP Patients And Approximately 2 Fold Greater in Either Dose of ACAMP Patients Than Placebo Patients (Controlled Long-Term Studies PRAMA and Paille)			
Preferred Term	ACAMP 1332 mg	ACAMP 1998/2000 mg	Placebo
Number of Patients	212	285	313
Number of Patients with an Adverse Event	126 (59%)	157 (55%)	164 (52%)
Pain	4 (2%)	4 (1%)	3 (<1%)
Flu Syndrome	1 (<1%)	10 (4%)	3 (<1%)
Nervousness	4 (2%)	4 (1%)	4 (1%)
Neurosis	4 (2%)	2 (<1%)	1 (<1%)
Convulsion	2 (<1%)	6 (2%)	1 (<1%)
Diarrhea	19 (9%)	34 (12%)	19 (6%)
Nausea	10 (5%)	6 (2%)	6 (2%)
Flatulence	1 (<1%)	5 (2%)	0
Weight Gain	2 (<1%)	16 (6%)	9 (3%)
Weight Loss	4 (2%)	5 (2%)	4 (1%)
Arthralgia	4 (2%)	3 (1%)	1 (<1%)
Source: Post-Text Table 8.8.6.7.0			

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Spontaneously Reported TEAEs by Treatment Duration

The table below displays AEs that show some trends over time, keeping in mind the fact that patients experiencing these events may have dropped out over time and that the small number of patients in the 3000 mg dose group, may complicate interpretation. Most notable is *diarrhea* which decrease impressively over time in both acamprosate dose groups and approaching placebo rates after approximately 2 months. *Abdominal pain, nausea and flatulence* appear to show a small decrease over time in the 1998/2000 mg dose group while incidence appears stable over time in the high dose acamprosate and placebo groups. *Dyspepsia* appears stable across all three groups but with a slightly higher incidence in the higher acamprosate dose group. *Hyperglycemia* and *hyperuricemia* tend to increase slightly over time in both acamprosate dose groups compared to placebo but more so at the higher dose suggesting a dose effect. *Eosinophilia* and *lymphocytosis* are present across periods in both acamprosate dose groups but not in placebo event though the number of patients effected is small. *Abnormal LFTs* is the only AE to show a trend toward a very small increase over time in both the acamprosate 1998/2000 mg and placebo groups but slightly more in the acamprosate group, while it remains stable over time for the acamprosate 3000 mg dose group.

Spontaneously Reported TEAEs by Treatment Duration (Study US 96.1)

	ACAMP 1998/2000 mg (n = 258)				ACAMP 3000 mg (n = 83)				Placebo (n =260)			
	0 - < 4 Weeks	4 - < 8 Weeks	8 - < 13 Weeks	≥ 13 Weeks	0 - < 4 Weeks	4 - < 8 Weeks	8 - < 13 Weeks	≥ 13 Weeks	0 - < 4 Weeks	4 - < 8 Weeks	8 - < 13 Weeks	≥ 13 Weeks
Number of Patients in Duration Interval	258	225	191	161	83	75	65	54	260	234	206	185
Number of Patients with an Adverse Event	174 (67%)	102 (45%)	92 (48%)	101 (63%)	61 (73%)	29 (39%)	31 (48%)	31 (57%)	168 (65%)	85 (36%)	92 (45%)	110 (59%)
Abdominal Pain	13 (5%)	2 (<1%)	1 (<1%)	0	2 (2%)	0	0	1 (2%)	6 (2%)	1 (<1%)	4 (2%)	1 (<1%)
Diarrhea	65 (25%)	17 (8%)	12 (6%)	6 (4%)	28 (34%)	9 (12%)	3 (5%)	2 (4%)	28 (11%)	7 (3%)	11 (5%)	9 (5%)
Nausea	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (5%)	1 (1%)	1 (2%)	2 (4%)	4 (2%)	2 (<1%)	0	8 (4%)
Liver Function Tests Abnormal	0	2 (<1%)	5 (3%)	9 (6%)	0	3 (4%)	0	2 (4%)	2 (<1%)	3 (1%)	3 (1%)	5 (3%)
Flatulence	17 (7%)	6 (3%)	1 (<1%)	1 (<1%)	2 (2%)	1 (1%)	1 (2%)	0	4 (2%)	1 (<1%)	2 (<1%)	2 (1%)
Dyspepsia	4 (2%)	1 (<1%)	2 (1%)	4 (2%)	4 (5%)	0	0	3 (6%)	4 (2%)	0	1 (<1%)	0
Hyperglycemia	1 (<1%)	5 (2%)	2 (1%)	3 (2%)	2 (2%)	1 (1%)	2 (3%)	3 (6%)	1 (<1%)	5 (2%)	4 (2%)	3 (2%)
Hyperuricemia	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (1%)	1 (2%)	2 (4%)	1 (<1%)	0	0	2 (1%)
Eosinophilia	0	2 (<1%)	2 (1%)	1 (<1%)	0	1 (1%)	0	0	0	0	0	0
Lymphocytosis	0	1 (<1%)	0	1 (<1%)	0	0	1 (2%)	0	0	0	0	0

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AEs Reported Using 43-Item Check List

Below is a table condensed from the sponsor's post-text table for controlled European short-term studies that collected AEs using a 43-item check list. The table below displays those AEs reported $\geq 2\%$ in either acamprosate dose group and approximately 2 fold greater in either acamprosate group compared to the placebo group. All of the AEs report an incidence at greater than 10% in either acamprosate dose group EXCEPT *confusion, urinary tract disorder, and metrorrhagia*. Every AE report shows a higher incidence in the 1332 mg dose group than the 1998/2000 mg dose group with a magnitude of at least approximately 2 fold. AEs that occurred at less than 2% in either acamprosate dose group would not be in the table below; no AEs were reported in the source post-text table at less than 2% in either acamprosate dose group except *metrorrhagia*. There were no AEs in the placebo group listing an incidence less than 2%. These high reporting rates compared to the rates observed for spontaneous collection of AEs may reflect the frequent questioning of participants by the investigators as they refer to the 43-item check list.

TEAEs Reported by 43-Item Checklist in $\geq 2\%$ Either ACAMP Dose And Approximately 2 Fold or Greater in ACAMP Patients Than Placebo Patients (Short-Term EUROPEAN Studies)			
Preferred Term	ACAMP 1332 mg	ACAMP 1998/2000 mg	Placebo
Number of Patients	135	434	518
Number of Patients with an Adverse Event	90 (67%)	213 (49%)	246 (47%)
Nervousness	46 (34%)	59 (14%)	86 (17%)
Libido Decreased	27 (20%)	44 (10%)	54 (10%)
Amnesia	24 (18%)	41 (9%)	44 (8%)
Paresthesia	24 (18%)	34 (8%)	40 (8%)
Vasodilatation	19 (14%)	21 (5%)	38 (7%)
Dizziness	18 (13%)	33 (8%)	37 (7%)
Confusion	8 (6%)	7 (2%)	13 (3%)
Asthenia	39 (29%)	61 (14%)	75 (14%)
Reaction Unevaluable	19 (14%)	36 (8%)	42 (8%)
Diarrhea	34 (25%)	61 (14%)	48 (9%)
Anorexia	23 (17%)	44 (10%)	48 (9%)
Sweating	23 (17%)	41 (9%)	47 (9%)
Abnormal Vision	15 (11%)	14 (3%)	26 (5%)
Palpitation	17 (13%)	23 (5%)	33 (6%)
Syncope	9 (7%)	7 (2%)	11 (2%)
Myalgia	17 (13%)	33 (8%)	35 (7%)
Urinary Tract Disorder	11 (8%)	14 (3%)	10 (2%)
Metrorrhagia	7 (5%)	5 (1%)	9 (2%)
Source: Post-Text Table 8.8.6.1.0			

Below is a table condensed from the sponsor's post-text table for controlled European long-term studies that collected AEs using a 43-item check list. The table below displays those AEs reported $\geq 2\%$ in either acamprosate dose group and approximately 2 fold greater in either acamprosate group compared to the placebo group. The notable AEs occurring at approximately greater than 10% in either acamprosate dose group is *abdominal pain, diarrhea, and abnormal vision*. The shaded AE, *taste perversion*, occurred at approximately 2 fold greater incidence in the 1988/2000 mg acamprosate group compared to the 1332 mg dose group which may suggest a dose response. AEs that occurred at less than 2% in either acamprosate dose group are not in the table below and are *skin disorder, urinary tract disorder and peripheral edema* which occurred at a rate of 1% only in the 1332 mg acamprosate dose group[. In the placebo group there were no AEs reported as zero. These high reporting rates compared to the rates observed for spontaneous collection of AEs may reflect the frequent questioning of participants by the investigators as they refer to the 43-item check list.

TEAEs Reported by 43-Item Adverse Event Checklist in $\geq 2\%$ Either ACAMP Dose And Approximately 2 Fold Greater in ACAMP Patients Than Placebo Patients (Controlled Long-Term EUROPEAN Studies)			
Preferred Term	ACAMP 1332 mg	ACAMP 1998/2000 mg	Placebo
Number of Patients	93	336	431
Number of Patients with an Adverse Event	58 (62%)	209 (62%)	250 (58%)
Abdominal Pain	8 (9%)	14 (4%)	17 (4%)
Diarrhea	16 (17%)	61 (18%)	43 (10%)
Abnormal Vision	8 (9%)	24 (7%)	21 (5%)
Taste Perversion	4 (4%)	22 (7%)	16 (4%)
Syncope	3 (3%)	9 (3%)	6 (1%)
Metrorrhagia	4 (4%)	8 (2%)	6 (1%)
Source: Post-Text Table 8.8.6.7.1			

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The table below was condensed from the sponsor's in-text table and compares polysubstance abusers with all patients in the US study, US 96.1. Shaded AEs identify 2 fold greater reporting rate compared to placebo in polysubstance users compared to event rates compared to placebo in the "all patients" group. Unfortunately the interpretation of this table is limited by the use of 'all patients' for comparison. Comparison to all non-polysubstance users would have provided a clearer effect of polysubstance use on these AEs.

Spontaneously Reported TEAEs in ≥ 3% of Patients and Approximately 2 Fold Greater in Acamp Group – From Study US 96.1				
(Shaded AEs identify 2 fold greater reporting rate compared to placebo in Polysubstance Users)				
Preferred Term	All Patients		Polysubstance Users	
	Acamp 1998/2000 mg N = 258	Placebo N = 260	Acamp 1998/2000 mg N = 40	Placebo N = 32
	n (%)	n (%)	n (%)	n (%)
Asthenia	11 (4%)	13 (5%)	4 (10%)	1 (3%)
Back Pain	12 (5%)	9 (3%)	4 (10%)	1 (3%)
Diarrhea	86 (33%)	48 (18%)	12 (30%)	8 (25%)
SGPT Increased	12 (5%)	14 (5%)	3 (8%)	1 (3%)
LFTs Abnormal	13 (5%)	10 (4%)	8 (20%)	2 (6%)
Flatulence	22 (9%)	8 (3%)	1 (3%)	2 (6%)
Dyspepsia	10 (4%)	6 (2%)	2 (5%)	0
Vomiting	10 (4%)	2 (<1%)	2 (5%)	1 (3%)
Hypertension	12 (5%)	5 (2%)	2 (5%)	2 (6%)
Hypertonia	7 (3%)	1 (<1%)	1 (3%)	0
Alcohol Intolerance	7 (3%)	5 (2%)	2 (5%)	1 (3%)

Source: In-Text Table 8.8.5.1.6.1

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The preferred AE terms listed below from the two tables, with and without baseline LFT elevations, do not appear to suggest a significant risk of hepatic or renal toxicity of acamprosate compared to placebo; but the sponsor should be asked to describe in greater detail the cases of *ascites, LFT abnormalities, cirrhosis, hepatitis, MI, angina, chest pain, eosinophilia, lab test abnormal, allergic reaction, and photosensitivity reaction*. The appearance of 5 MI on acamprosate and none on placebo requires further investigation.

Spontaneously Reported TEAEs in Patients With and Without Abnormal LFTs at Baseline (All Controlled-Studies)				
	Without clinically significant abnormal LFTs at baseline		With clinically significant abnormal LFTs at baseline	
	Pooled ACAMP	Placebo	Pooled ACAMP	Placebo
Number of patients	968	774	302	234
Patients with an AE	665 (69%)	497 (64%)	196 (65%)	158 (68%)
Diarrhea	219 (23%)	94 (12%)	45 (15%)	30 (13%)
Flatulence	46 (5%)	13 (2%)	12 (4%)	7 (3%)
Ascites	1 (<1%)	0	1 (<1%)	1 (<1%)
LFTs Abnormal	12 (1%)	4 (<1%)	6 (2%)	6 (3%)
Liver cirrhosis	1 (<1%)	0	NR	NR
Hepatitis	2 (<1%)	0	NR	NR
MI	2 (<1%)	0	3 (1%)	0
Angina Pectoris	5 (<1%)	4 (<1%)	0	1 (<1%)
Chest Pain	10 (1%)	7 (<1%)	1 (<1%)	4 (2%)
Eosinophilia	4 (<1%)	0	2 (<1%)	0
Bilirubinemia	5 (<1%)	6 (<1%)	1 (<1%)	0
SGPT increased	11 (1%)	9 (1%)	4 (1%)	6 (3%)
SGOT increased	10 (1%)	11 (1%)	6 (2%)	5 (2%)
Alk Phos increased	1 (<1%)	1 (<1%)	2 (<1%)	0
GGT increased	1 (<1%)	2 (<1%)	2 (<1%)	0
LDH Increased	1 (<1%)	0	1 (<1%)	0
Creatinine increased	1 (<1%)	1 (<1%)	NR	NR
BUN increased	0	1 (<1%)	NR	NR
Lab test abnormal	5 (<1%)	2 (<1%)	2 (<1%)	0
Allergic reaction	8 (<1%)	7 (<1%)	1 (<1%)	0
Photosensitivity reaction	0	1 (<1%)	1 (<1%)	0
NR = none reported	Post-Text Table 8.8.16.0.1		Post-Text Table 8.8.16.0.0	
Sponsor's Definition of Clinically Significant LFTs: Total Bilirubin > 2X ULN AST > 3X ULN ALT > 3X ULN GGT > 3X ULN Alk Phos > 3X ULN LDH > 3X ULN				

RECOMMENDATIONS:

For recommendations please refer to the review section, Overall Summary Statements of Findings and Recommendations.

ATTACHMENT 1

Group I – Double-Blind, Placebo-Controlled Studies in Alcohol-Dependent Patients In the Integrated Summary of Safety – Safety Population												
Study # (Common Name) (Country) (Shaded Rows = ≥ 150 Patients In the 1998/2000 mg Group)	Total Patients	Daily Acamprostate Dose				Treatment Duration ¹	Follow-Up Duration	Adverse Event Reporting		Vital Signs ²	Clinical Lab Assess- ments	ECG ³
		1332 mg	1998/ 2000 mg	3000 mg	Placebo			Reported Spontaneously	Reported by Checklist ¹			
Double-Blind, Placebo-Controlled Short-Term Studies												
ACAMP/US/96.1 (US 96.1) (United States)	601		258	83	260	6 months (24 weeks)	8 weeks	X		X	X	X
AOTA/B/90.3 (Pelc II) (Belgium/France)	188	63	63		62	90 days (13 weeks)	None		X ⁴	X	X	
AOTA/I/89.4 (Poldrugo) (Italy)	246	31*	91*		124	180 days (26 weeks)	26 weeks		X ⁴	X	X	
AOTA/I/90.1 (Tempesta) (Italy)	330		164		166	180 days (26 weeks)	12 weeks		X ⁴		X	
AOTA/LP90/N001 (UKMAS) (United Kingdom)	581		289		292	24 weeks	None	X		X	X	X
AOTA/NL/91.1; AOTA/B/90.2 (BENELUX) (Belgium, The Netherlands)	262	32*	96*		134	180 days (26 weeks)	26 weeks		X	X	X	
AOTA/E/91.1 (ADISA) (Spain)	295		147		148	180 days	None	X		X	X	
AD 04 089 (Ladewig) (Switzerland)	61	9*	20*		32	180 days (26 weeks)	26 weeks		X ⁴		X	
Short-Term SUB-TOTAL	2564	135	1128	83	1218							
Double-Blind, Placebo-Controlled Long-Term Studies												
AOT 411.198 (PRAMA) (Germany)	272	24*	112*		136	48 weeks	48 weeks	X		X	X	
544 (Paille) (France)	538	188	173		177	360 days (51 weeks)	24 weeks	X		X	X	
AD 10 089 (Lesch) (Austria)	448	34*	190*		224	360 days (51 weeks)	52 weeks		X	X	X	
AOTA/P/89.1 (Barrias) (Portugal)	302	48*	102*		152	360 days (51 weeks)	26 weeks		X ⁴	X	X	
AA 11 088 (Besson) (Switzerland)	110	11*	44*		55	360 days (51 weeks)	52 weeks		X ⁴	X	X	
Long-Term SUB-TOTAL	1670	305	621		744							
Totals	4234	440	1749	83	1962							
Source: Adapted from In-Text Tables 8.8.1.3.1; 8.8.1.3.2												

¹The checklist consisted of a 43-item questionnaire.

²Vital sign measurements included at least one of the following: systolic and diastolic blood pressure, heart rate, and body weight. Vital sign data are not included in the ISS database, except for US 96.1, Pelc II, PRAMA, and Paille. Vital sign data for the other European studies will be discussed based on results in the final study reports.

³Studies with baseline and postbaseline ECG data.

⁴Spontaneously reported adverse events were collected by the site. However, the adverse event was only recorded on the CRF if listed on the checklist. Otherwise, it was recorded as "other" with no textual description.

Note: Total Patients is based on the Safety Population.

Note: The US 96.1 study used 500 mg acamprosate tablets. Patients in the 2000 mg acamprosate group received two 500 mg acamprosate tablets b.i.d.; patients in the 3000 mg acamprosate group received three 500 mg acamprosate tablets b.i.d. The European studies used 333 mg acamprosate tablets. Patients in the 1332 mg acamprosate group received two 333 mg

acamprosate tablets in the morning, and one 333 mg acamprosate tablet at mid-day and in the evening. Patients in the 1998 mg acamprosate group received two 333 mg acamprosate tablets t.i.d.

Note: Patients from Poldrugo, BENELUX, Ladewig, PRAMA, Lesch, Barrias, and Besson (denoted by "**") were categorized based on body weight (≤ 60 kg or >60 kg). Patients with a body weight ≤ 60 kg who

were randomized to the acamprosate group received 1332 mg acamprosate daily. Patients with a body weight >60 kg who were randomized to the acamprosate group received 1998 mg acamprosate daily.

Note: Studies with a treatment phase that was longer than six months (26 weeks) are included in the long-term studies classification.

Note: Duration was specified by months, weeks, or days for each study. Duration by weeks (rounded to the nearest whole number) is provided for those studies in which duration was not specified by weeks.

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ATTACHMENT 2 (Source: In-Text Table 8.8.5.2)

43-item Checklist	COSTART Preferred Term
DECREASED APPETITE	ANOREXIA
GASTRALGIA	DYSPEPSIA
CONSTIPATION	CONSTIPATION
DIARRHOEA	DIARRHEA
NAUSEA	NAUSEA
VOMITING	VOMITING
ABDOMINAL PAIN	ABDOMINAL PAIN
PRURITUS	PRURITUS
OTHER SKIN PROBLEMS	SKIN DISORDER
LUMBAR PAIN	BACK PAIN
MUSCULAR PAIN	MYALGIA
VISION DISTURBANCE	ABNORMAL VISION
DRYNESS OF MOUTH	DRY MOUTH
SWEATING	SWEATING
PINS AND NEEDLES	PARESTHESIA
DIZZINESS	DIZZINESS
FAINING	SYNCOPE
SHIVERING	CHILLS
BITTER TASTE IN MOUTH	TASTE PERVERSION
EXCITEMENT, TENSION	AGITATION
HUMMING IN THE EAR	TINNITUS
DAYTIME SLEEPING	SOMNOLENCE
DIFFICULTY GETTING TO SLEEP	INSOMNIA
WAKING IN MIDDLE OF NIGHT	INSOMNIA
WAKING EARLY	INSOMNIA
OVERSLEEPING	SOMNOLENCE
HEADACHE, HEAVY HEAD	HEADACHE
MEMORY PROBLEMS	AMNESIA
CONFUSION	CONFUSION
DIFFICULTY CONCENTRATING	THINKING ABNORMAL
INADEQUATE SLEEP	INSOMNIA
HOT FLUSHES	VASODILATATION
MICTURITION PROBLEMS	URINARY TRACT DISORDER
DECREASED LIBIDO	LIBIDO DECREASED
FRIGIDITY OR IMPOTENCE	IMPOTENCE
INCREASED LIBIDO	LIBIDO INCREASED
GALACTORRHOEA	MALE LACTATION or FEMALE LACTATION
PERIODS IRREGULAR	METRRORRHAGIA
PALPITATIONS	PALPITATION
PRECORDIAL PAIN	CHEST PAIN SUBSTERNAL
OEDEMA LOWER LIMBS	PERIPHERAL EDEMA
DYSPNOEA	DYSPNEA
TIREDNESS	ASTHENIA
OTHER	REACTION UNEVALUABLE

ATTACHMENT 3

In-Text Table 8.8.1.3:3 Studies NOT Included in the Integrated Database for the Integrated Summary of Safety

Study # (Common Name) (Study Type)	Total Volunteers/ Patients	Daily Acamprosate Dose/Placebo/Active Comparator	Comments
Group II – CLINICAL PHARMACOLOGY STUDIES			
1. Pharmacokinetic/ADME Studies			
— LPA125/89391 (Chasseaud) (PK/Metabolism/Radiolabelled)	2	1320 mg ³⁵ S	Healthy volunteers; single dose
— 7488, C 37646 (Scott) (Radiolabelled/Metabolism/ADME)	4	1320 mg ¹⁴ C	Healthy volunteers; single dose
ACAMP/F/98.02 (Caplain) (IV PK)	12	333 mg IV	Healthy volunteers; single dose
2. Pharmacodynamic/Pharmacokinetic Studies: Dose/Rising Dose Studies			
MERAM 27 Oct 1986 (Boismare) (Rising Dose/PD/Tolerance)	10	750 mg, 1500 mg, 2250 mg, 3000 mg	Healthy volunteers; no concomitant medications; 3 days each dose level; total duration of treatment was 12 days
89027 (Weber) (Bioavailability)	6	666 mg, 1332 mg	Healthy volunteers; open label; single and multiple dose; tablets and aqueous solution
RD298/17163 (Dewland I) (Rising Dose/PD/GI Tolerance)	18	1332 mg, 2664 mg, 3996 mg, 5328 mg, placebo	Healthy volunteers; 12 patients received 2 dose levels of acamprosate; 7 days of treatment
RD298/17927 (Dewland II) (Rising Dose/PK/PD/Tolerance)	6	333 mg, 666 mg, 1332 mg, 2664 mg	Healthy volunteers; single rising dose
SS409 (Theodore II) (Rising Dose/PK)	62	600 mg, 1000 mg, 1600 mg, 2000 mg	Healthy volunteers; multiple doses; oral solution; 8 days of treatment
MERAM 6 Feb 1991 (Jaillon) (PK/PD/Rising Dose/Tolerance/IV Administration)	12	10, 20, and 30 mg/kg IV	Healthy volunteers; single dose
AD875H (Fourtillan II) (PK)	24	666 mg, 1998 mg	Healthy volunteers; single vs. multiple doses
3. Pharmacokinetic Studies: Effects of Food			
AD1011H (Fourtillan IV) (PK/Food Interaction)	12	999 mg	Healthy volunteers; fasted vs. non-fasted; single dose
4. Pharmacokinetics: Male vs. Female and Special Populations			
RD298/20673 (Dewland IV) (Male vs. Female PK)	24	666 mg	Healthy volunteers; single dose
AOTA-CIN PA1-AD1054H (Pelc III) (PK/Post-Alcohol Withdrawal)	9	1998 mg	Alcohol-dependent patients post-alcohol withdrawal; 3 months of treatment
AOTA-CIN-IR1-AD1003H (Sennesael) (PK/Renal Impairment)	12	666 mg	Healthy volunteers vs. subjects with impaired renal failure; single dose
AOTA-CIN IHP1 (Miguet) (PK/Hepatic Impairment)	6	666 mg	Patients with chronic/acute hepatic failure of alcohol origin; single dose
90235 (Haug) (PK/Hepatic Impairment)	12	1998 mg	Patients with impaired hepatic function due to alcoholism; 7.3 days of treatment
5. Pharmacokinetic Studies: Drug Interactions			
12/89-03 AL (Lucker) (PK/Ethyl Alcohol Interaction)	12	1998 mg	Healthy volunteers; 2.3 days of treatment
RD298/17949 (Dewland III) (PK/Ethyl Alcohol Interaction)	12	1332 mg	Healthy volunteers; alcohol vs. no alcohol; single dose
RD298/20828 (Dewland V) (Disulfiram Interaction)	20	1998 mg, disulfiram 500 mg	Healthy volunteers; 14 days of acamprosate treatment including 7 days with disulfiram; crossover to 7 days of disulfiram treatment
AD1126H (Decourt I) (Diazepam Interaction)	16	1998 mg, diazepam 10 mg	Healthy volunteers; 14 days of diazepam treatment including 7 days with acamprosate; crossover to 7 days of acamprosate treatment

In-Text Table 8.8.1.3:3

Studies NOT Included in the Integrated Database for the Integrated Summary of Safety (Cont'd)

Study # (Common Name) (Study Type)	Total Volunteers/Patients	Daily Acamprosate Dose/Placebo/Active Comparator	Comments
5. Pharmacokinetic Studies: Drug Interactions (cont'd)			
AD1135H (Decourt II) (Imipramine Interaction)	16	1998 mg, imipramine 50 mg	Healthy volunteers; 10 days of acamprosate treatment including 1 day of imipramine treatment; crossover to 1 day of imipramine treatment
ACAMP/US/97.1 (US 97.1) (Naltrexone/PK)	24	2000 mg, naltrexone 50 mg	Healthy volunteers; acamprosate vs. naltrexone; double-blind 3-way crossover; 7 days of treatment
6. Pharmacodynamic Studies: CNS Effects			
MERAM 16 Oct 1986 (Poenaru) (CNS/Sleep Study)	14	1332 mg	Healthy volunteers; 15 days of treatment
AFB 06/0081-89 (Hermann) (PD/CNS/Sleep/Tiredness/Psychometric Tests/EEG)	16	400 mg, 800 mg, placebo, diazepam 10 mg	Healthy volunteers; single dose; crossover
19 Oct 1987 (Moser I) (PD/Driving Performance)	13	666 mg, placebo, diazepam 10 mg	Healthy volunteers; single dose; crossover;
6 Nov 1987 (Moser II) (PD/Driving Performance)	24	666 mg, placebo, diazepam 10 mg	Healthy volunteers; single dose; crossover; with 0.75/kg alcohol/dose
ACAMP/F/95.1 (Macher I) (CNS Effects/Magnetic Resonance Spectroscopy)	8	15 mg/kg IV	Healthy volunteers; double-blind; placebo-controlled; crossover
ACAMP/F/96.1 (Macher II) (PD/Sleep/Driving Performance/Body Sway)	18	1998 mg	333 mg acamprosate tablets; double-blind; placebo-controlled; crossover; naltrexone comparator
ACAMP/F/98.1 (Macher III)** (CNS Pharmacodynamics)	24	1998 mg, placebo	Alcohol-dependent patients; 3 weeks of treatment; double-blind, placebo-controlled
COMBINE Pilot I (Pilot I)* (Combining Medications and Behavioral Interventions; NIAAA Sponsored)	23	2000 mg, 3000 mg; 50 mg and 100 mg naltrexone, placebo	Alcohol-dependent patients; 21 days of treatment; double-blind; placebo-controlled; 4-way cross-over; acamprosate and naltrexone alone and combined
7. Pharmacodynamic: Other			
AOTA/S/91.1 (Borg) (Biological Markers for Abstinence)	10	1998 mg; placebo	Alcohol-dependent patients; double-blind; placebo-controlled; 26 weeks of treatment
9225 (O'Malley)** (Acamprosate Laboratory Study)	7	1500 mg, 3000 mg	Alcohol-dependent patients; 11 days of treatment; double-blind; placebo-controlled
8. Bioequivalence/Bioavailability			
AD864H (Fourtillan I)	6	666 mg	Healthy volunteers; aqueous solution vs. tablets; single dose
AD993H (Fourtillan III) (Bioequivalence)	12	333 mg	Healthy volunteers; open label; single; crossover, bioequivalence of PK for 333 mg reference and new formulation tablets
AD1044H (Fourtillan V) (Bioavailability)	16	1998 mg	Healthy volunteers; open label; single dose; crossover; bioavailability of PK for 333 mg reference and new formulation tablets
SS401 (Theodor I) (Bioequivalence/Bioavailability)	24	1998 mg, 2000 mg	Healthy volunteers; open label; 9 days of treatment with crossover; bioequivalence/bioavailability to compare PK of 333 mg and 500 mg acamprosate tablets
TOTAL	489		

In-Text Table 8.8.1.3:3

Studies NOT Included in the Integrated Database for the Integrated Summary of Safety (Cont'd)

Study # (Common Name) (Study Type)	Total Volunteers/ Patients	Daily Acamprostate Dose/Placebo/Active Comparator	Comments
Group III - EARLY CLINICAL EXPERIENCE STUDIES			
Hillemand I (1982-1983) (Dose Response)	85	1000 mg, 1500 mg, 1750 mg, 2000 mg, 2250 mg, placebo	Alcohol-dependent patients; double-blind; placebo-controlled; 90 days of treatment; acamprostate administered by body weight (25 mg/kg); 250 mg acamprostate tablets
Lhuintre (1984-1986) (Post-Detoxification)	569	1332 mg, placebo	Alcohol-dependent patients; double-blind; placebo-controlled; 90 days of treatment; 90 days of follow-up; 333 mg acamprostate tablets
Poinso (1986) (Dose Response)	30	750 mg, 1000 mg, 1500 mg	Alcohol-dependent patients; 90 days of treatment; 250 mg acamprostate capsules
Roussaux (1987-1989)	127	1332 mg, 1998 mg	Alcohol-dependent patients; double-blind; placebo-controlled; 90 days of treatment; no follow-up
Hillemand II (1988) (Dose Response)	11	750 mg	Alcohol-dependent patients; open label; 90 days of treatment; 250 mg acamprostate tablets
AA11087 (Pelc I) (Post-Detoxification)	102	1332 mg, 1998 mg placebo	Alcohol-dependent patients; double-blind; placebo-controlled; 180 days of treatment; no follow-up
TOTAL	924		
Group IV - PHASE IV STUDIES			
MERAM Phase IV (8 Jan 1991); (Post-Withdrawal)	860	1332 mg	Alcohol-dependent patients; 3 months (12 weeks) of treatment; open label
AOTA/F/91.6 (ASATIM) (Co-Administration of Detoxification Medication; France)	591	1998 mg	Co-Administration of Atrium, Equanil, and Seresta; Alcohol-dependent patients; 15 days (2 weeks) of treatment
CAMP/B/95.1 (NEAT: Belgium) (Psychological Intervention)	614	1332 mg, 1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
CAMP/B/95.1 Extension (NEAT: Belgium) (Psychological Intervention)	147	1332 mg, 1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
CAMP/CH/95.1 (NEAT: Switzerland) (Psychological Intervention)	105	1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
CAMP/A/95.1 (NEAT: Austria) (Psychological Intervention)	111	1332 mg, 1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
CAMP/GB/95.1 (NEAT: UK) (Psychological Intervention)	227	1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
CAMP/P/95.1 (NEAT: Portugal) (Psychological Intervention)	234	1332 mg, 1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
ACAMP/D/96.1 Integral (Psycho-Social Support)	753	1332 mg, 1998 mg	Alcohol-dependent patients; 6 months (24 weeks) of treatment; open label
ACAMP/F/97.1 (ADES)	133	1998 mg, 2000 mg	Alcohol-dependent patients; 2 months (8 weeks) of treatment; open label
CAMP/B/96.1 (CAPRISO)* (Follow-Up Comparison)	35	1998 mg	Alcohol-dependent patients; 3 months of treatment; open label

In-Text Table 8.8.1.3:3

Studies NOT Included in the Integrated Database for the Integrated Summary of Safety (Cont'd)

Study # (Common Name) (Study Type)	Total Volunteers/ Patients	Daily Acamprosate Dose/Placebo/Active Comparator	Comments
Group IV - PHASE IV STUDIES (cont'd)			
CAMP/NL/96.1 (MICADO)* (Psychological Intervention)	248	1998 mg	Alcohol-dependent patients; 6 months of treatment; open label
ACAMP/Pharm Eco/Fr/97.03 (A.R.E.S.)* (Pharmacoeconomics)	400	1998 mg	Alcohol-dependent patients; 12 months of treatment; open label
CAMP 98/01 (DATA)* (Pharmacoepidemiologic)	1676	1332 mg, 1998 mg	Alcohol-dependent patients; 14 weeks of treatment; open label
ACAMP/GB/97.1 (Nutt) (Psychological Intervention)***	26	1998 mg	Alcohol-dependent patients; 3 months (12 weeks) of treatment; open label
TOTAL	6,160		
ONGOING/INCOMPLETE PLACEBO-CONTROLLED STUDIES			
CAMP/D/99.1 (A.P.D.T)** (Acamprosate Pre-Detoxification Treatment)	200 planned; 9 entered	1332 mg	Alcohol-dependent patients; 13 weeks of treatment; double-blind, placebo-controlled
COMBINE Pilot 3 (Pilot 3)** (Combining Medications and Behavioral Interventions; NIAAA Sponsored)	108 planned; 101 entered	3000 mg; 25 mg and 100 mg naltrexone	Alcohol-dependent patients; 16 weeks of treatment; acamprosate and naltrexone alone and combined with 3 behavioral therapies
TOTAL	110		

* Study completed; data analysis ongoing.

** Study ongoing.

*** Study terminated due to poor recruitment.

Note: All studies were conducted in Europe with the exception of US 97.1, O'Malley (9225), COMBINE Pilot 1, and COMBINE Pilot 3, which were conducted in the United States (US).

Note: Data will be discussed as available from final study reports. Data from studies with final reports completed as of 31 July 2001 will be included in the ISS.

Note: NEAT = New European Alcoholism Treatment

Note: The European studies used 333 mg acamprosate tablets. Patients in the 1332 mg acamprosate group received two 333 mg acamprosate tablets in the morning, and one 333 mg acamprosate tablet at mid-day and in the evening. Patients in the 1998 mg acamprosate group received two 333 mg acamprosate tablets t.i.d. When both doses are shown, this denotes that patients were categorized according to body weight (≤ 60 kg or > 60 kg). Patients with a body weight ≤ 60 kg who were randomized to the acamprosate group received 1332 mg acamprosate daily. Patients with a body weight > 60 mg who were randomized to the acamprosate group received 1998 mg acamprosate daily.

Note: Duration was specified by months, weeks, or days for each study. Duration by weeks (rounded to the nearest whole number) is provided for those studies in which duration was not specified by weeks.

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ATTACHMENT 4

Patient-Weeks of Treatment Exposure

Short-Term Studies

Study	Placebo	ACAMP 1332	ACAMP 1998/2000	ACAMP 3000	ACAMP Pooled
ADISA	2942.3		3019.6		5961.9
BENELU X	1622.9	378.3	1468.4		3469.6
Ladewig	639.9	122.7	456.1		1218.7
Pelc II	582.3	666.9	708.4		1957.6
Poldrugo	1505.1	540.6	1361.4		3407.1
Tempesta	3481.3		3493.6		6974.9
UKMAS	4356		4094.9		8450.9
US 96.1	4623.1		4042.0	1398.1	10063.2
Totals	19752.9	1708.5	18644.4	1398.1	41503.9

Long-Term Studies

Entire Study Duration

Study	Placebo	ACAMP 1332	ACAMP 1998/2000	ACAMP Pooled
Barrias	5697.6	1849.4	3977.3	11524.3
Besson	1523.6	283.4	1241.7	3048.7
Lesch	5868.6	1029.7	5234.9	12133.2
PRAMA	3547.3	785.6	3598.1	7931.0
Paille	5597.6	6637.0	6525.9	18760.5
Totals	22234.7	10585.1	20577.9	53397.7

First 26 Weeks of Treatment Exposure

Study	Placebo	ACAMP 1332	ACAMP 1998/2000	ACAMP Pooled
Barrias	3361.1	1065.7	2322.1	6748.9
Besson	954.6	210.3	749.9	1914.8
Lesch	3542.4	584.9	3166.9	7294.2
PRAMA	2211.6	471.6	2159.9	4843.1
Paille	3509.4	3952.1	3733.4	11194.9
Totals	13579.1	6284.6	12132.2	31995.9

Treatment Exposure after First 26 Weeks

Study	Placebo	ACAMP 1332	ACAMP 1998/2000	ACAMP Pooled
Barrias	2336.4	783.7	1655.1	4775.2
Besson	569	73.1	491.9	1134.0
Lesch	2326.1	444.9	2068.0	4839.0
PRAMA	1335.7	314.0	1438.3	3088.0
Paille	2088.1	2684.9	2792.4	7565.4
Totals	8655.3	4300.6	8445.7	21401.6

ATTACHMENT 5

Patient-Weeks of Treatment Exposure in the Phase IV Studies

	Dose	1332	1998	Total
	unknown	mg/day	mg/day	
NEAT – UK		1798.00	324.00	2122.00
NEAT – Belgium		1882.00	6562.00	8444.00
NEAT – Switzerland			1834.00	1834.00
NEAT – Austria	32.00	204.00	1772.00	2008.00
NEAT – Portugal		986.00	3226.00	4212.00
NEAT – Belgium Extension		1303	4877	6180.00
ASATIM			1214.00	1214.00
Integral	47.71	1893.86	10480.43	12422.00

Meram Phase IV	1332
	mg/day
Patients Enrolled	860
Patients with Eval for Prim Eff, D30	827
Patients with Eval for Prim Eff, D60	741
Patients with Eval for Prim Eff, D90	639
Patient-Weeks of Study Duration	9463.29

ADES	1998	2000
	mg/day	mg/day
Patients	68	65
Withdrawal interval 1-7 days	3	6
Withdrawal interval 8-28 days	2	5
Withdrawal interval 29-56 days	8	6
Completed, disc dose after V3	2	2
Other completed patients	53	46
Patient-Weeks of Study Duration	468.14	407.71

	1332	1998	2000	Unk	All	All
	mg/day	mg/day	mg/day	1332/199	1332/1998	patients
Total Phase IV Duration	17530.14	30757.57	407.71	79.71	48367.43	48775.14

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PHASE IV DISCONTINUATIONS – BASIS FOR CALCULATION OF PATIENT-WEEKS OF EXPOSURE

NEAT Studies (excluding Belgium Extension)

Patient-weeks of exposure are based on a database from Lipha France; totals for all doses combined are similar to those calculated using mean exposure in the reports.

NEAT Belgium Extension

Patient-weeks of exposure are based on report, assumption was made that the overall mean exposure was also the mean exposure for both dose groups.

ASATIM

Patient-weeks of exposure are based the duration of treatment frequency located in Table 42 in the report.

Integral

Patient-weeks of exposure are based on a database from Lipha France.

Meram Phase IV Study

Patient-weeks of exposure are calculated using the number of subjects who were evaluated for primary efficacy. Patients with evaluations at Day 90 are considered to have 90 days of exposure, patients with evaluations at Day 60 but not Day 90 are considered to have 60 days of exposure, patients with evaluations at Day 30 but not Day 60 are considered to have 30 days of exposure, and patients who were enrolled but do not have an evaluation at Day 30 are considered to have 1 day of exposure.

ADES

Patient-weeks of exposure are calculated using the withdrawal interval and completion status. Patients who completed the study but discontinued dose after Visit 3 are considered to have 29 days of exposure, and all other completers are considered to have been exposed for the full 8 weeks (56 days). Patients who withdrew in the interval 1 to 7 days were assigned an exposure of 1 day, patients who withdrew in the interval 8 to 28 days were assigned an exposure of 8 days, and patients who withdrew in the interval 29 to 56 days were assigned an exposure of 29 days.

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ATTACHMENT 6

In-Text Table 8.8.8.0:1

Deaths that Occurred During Treatment Phase in the Controlled Studies

Treatment	Study	Patient	Gender	Age	Cause of Death
Acamprosate 1332 mg/day	PRAMA	168	Female	35	Severe craniocerebral trauma
Acamprosate 1332 mg/day	Paille	307	Male	41	Car crash
Acamprosate 1332 mg/day	Paille	485	Male	46	Haematemesis
Acamprosate 1998/2000 mg/day	Poldrugo	1	Male	64	Atrial fibrillation
Acamprosate 1998/2000 mg/day	Lesch	106	Male	56	Suicide by ingestion of massive doses of meclobamides. Body found by police 12 days after last study visit (reason for withdrawal from study was reported as death). ¹
Acamprosate 1998/2000 mg/day	Lesch	183	Male	47	Death by natural cause (circa 1 month after he started the study). The study medication box was found indicating that the patient did not take any study medication.
Acamprosate 1998/2000 mg/day	PRAMA	236	Male	33	Suicide (strangulation)
Acamprosate 1998/2000 mg/day	Paille	282	Male	55	Mesenteric infarction
Acamprosate 1998/2000 mg/day	UKMAS	297	Male	61	Acute subdural hemorrhage
Acamprosate 1998/2000 mg/day	Paille	319	Male	57	Accidental fall
Acamprosate 1998/2000 mg/day	Besson	1054	Male	53	Suicide
Acamprosate 1998/2000 mg/day	Barrias	2023	Male	34	Cardiac failure
Placebo	Paille	22	Male	42	Motorbike crash
Placebo	Ladewig	32	Male	44	Suicide 2 days after withdrawing from the study.
Placebo	PRAMA	203	Female	42	Suicide
Placebo	UKMAS	227	Male	34	Accidental fall, fatal intracranial hemorrhage, and fractured skull
Placebo	Paille	342	Male	40	Accidental fall
Placebo	Lesch	337	Male	50	Cardiac failure
Placebo	Besson	2060	Male	51	Cardiac arrest
Placebo	Barrias	3072	Male	45	Left ventricular hypertrophy due to an alcohol induced cardiomyopathy

Data source: Table 8.8.9.0.0

ND: No data are available.

¹ This patient was included despite the death being reported 12 days after last study visit because the exact day of death is unknown.

Additional Deaths Not in the table above.

Placebo UKMAS 484 Male 51 Liver failure

Acamprosate Barrias 63 Male 44 Cardiac arrest the day following hospitalization for severe pneumonia and uncontrolled insulin dependent diabetes

ATTACHMENT 7**In-Text Table 8.8.8.0:2****Deaths that Occurred During the Clinical Pharmacology, Early Clinical Experience, and the Phase IV Studies**

Treatment	Study	Subject	Gender	Age	Cause of Death
Acamprosate	NEAT Extension	1	Female	38	Suicide: primary cardiac arrhythmia followed by cardiogenic shock.
Acamprosate	NEAT UK	2	Male	36	Variceal bleeding
Acamprosate	NEAT Portugal	3	Male	38	Massive alcohol intoxication
Acamprosate	NEAT Belgium	5	Male	43	Acute necrotic pancreatitis
Acamprosate	NEAT Belgium	7	Male	45	Sudden death
Acamprosate	NEAT Belgium	9	Female	39	Trauma
Acamprosate	NEAT Belgium	12	Female	48	Homicide
Acamprosate	NEAT Belgium	13	Male	37	Suicide
Acamprosate	Lhuintre	1111	Male	57	Decompensation of cirrhosis
Acamprosate	Integral	81004	Male	37	Heart and circulatory failure together with an asthma attack
Acamprosate	Meram Phase IV	ND	ND	ND	Accident
Acamprosate	Meram Phase IV	ND	ND	ND	Suicide
Acamprosate	Meram Phase IV	ND	ND	ND	Cirrhosis
Acamprosate	Meram Phase IV	ND	ND	ND	Surgical complications
Placebo	Lhuintre	2120	Male	46	Cerebrovascular accident
Placebo	Lhuintre	3322	Male	71	Accidental fall

ND: No data are available

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/s/

Michael Sevka
6/10/02 06:05:17 PM
MEDICAL OFFICER

Bob Rappaport
6/10/02 06:09:21 PM
MEDICAL OFFICER

I concur with Dr. Sevka's conclusions and recommendations.

NDA 21-431

ACAMPROSATE

Submission Received: December 27, 2001

PDUFA Goal Date: June 27, 2002

Sponsor: Lipha Pharmaceuticals, Inc.

Review of Safety for Laboratory Values, ECG's, Vital Signs, Post-marketing Safety data, Deaths, Overdoses, and Withdrawal due to Adverse Events

Chuck Cooper, MD

MEDICAL OFFICER SAFETY REVIEW

The following safety review consists of a detailed evaluation of specific safety aspects of the acamprosate NDA review (NDA 21-431). Review and analysis contained in this section pertain to the following: laboratory values, ECG's, vital signs, post-marketing safety data, deaths, overdoses, and withdrawals due to adverse events.

The conclusions and recommendations contained in this review will be used by the primary Medical Officer reviewer to assist in making a final risk:benefit assessment and recommendation regarding this application.

LABORATORY REVIEW

Coagulation Parameters

The sponsor did not submit any analysis or summary tables for coagulation laboratory values. Because of specific SAE's/Deaths which involved bleeding during some of the studies, an analysis of coagulation parameters was performed. The following analysis was done by the Medical Officer using data obtained from the sponsor submitted SAS transport file, SS_LABAN.xpt. which contains laboratory data from the 13 key double-blind, placebo controlled clinical trials. Studies 10 (PRAMA) and 17 (ADISA) are the only studies which measured coagulation laboratory values, and PT was the only coagulation parameter measured. In these two studies, there were a total of 554 patients who had PT's drawn, 261 patients from study 10, and 293 in study 17.

Study 17

Of the 293 patients who had PT's drawn in Study 17, 72 had only a single PT done of which 2 were abnormally elevated. In these patients, it is not possible to determine what effect acamprosate may have had on coagulation because follow-up testing was not done.

In total, there were 221 patients who had 2 or more PT's measured (113 in the acaprosate arm and 108 in the placebo arm). This includes 33 patients who had PT measured twice (28 on days 0 and 90; 5 on days 0 and 180), 182 who had PT measured three times, and 6 patients who had PT measured 4 times. Of the patients who had more than one measurement, there were 29 who had elevated PT values including 11 (9.7%) in the acamprosate arm and 18 (16.7%) in the placebo arm with elevated PT's.

Examination of the pattern of PT's revealed that in the placebo arm, 8 had PT's that increased over the course of the study, 5 had PT's that decreased over the course of the study, and 5 did not have a trend of increasing or decreasing (these were mostly up and down without a pattern). For the acamprosate arm, there were 4 whose PT pattern increased, 4 whose PT pattern decreased, and 3 whose PT pattern did not have a trend of increasing or decreasing (mostly up and down).

With regard to the degree of abnormality, there were 31 patients in Study 17 who had PT measurements which ranged from 120-153% of the upper limit of the normal range. No patient had a PT which was greater than 153% of the upper limit of the normal range and the abnormal results were, for the most part, distributed evenly throughout the abnormal range. There were no significant differences between the two treatment arms with regard to the degree of abnormality of the elevated PT measurements.

Study 10

There were a total of 261 patients who had PT's drawn in study 10. Of these patients, 33 had only one PT measurement done during the course of the study (31 at visit 0 and 2 at visit 1). In these patients, it is not possible to determine what effect acamprosate may have had on coagulation because follow-up testing was not done. 44 patients had 2 measurements done. However, 39 of these patients had their PT measurements done early in the course of the study (visits 0 and 1), and, therefore, may not be useful in assessing the effect of long term administration of acamprosate.

Of the 261 total patients who had PT's drawn in study 10, 77 had too few measurements to determine a trend (either 1 total measurement or 2 both very early in the treatment course). None of these 77 had significant severe abnormalities in the measured PT.

There were 184 patients who had 3 or more PT's measured including 101 patients in acamprosate arm and 83 patients in the placebo arm. Of these 184 patients, 60 had abnormally elevated PT's including 37 (36.6%) in the acamprosate arm and 23 (27.7%) in the placebo arm.

Examination of the pattern of PT's revealed that in the placebo arm, 6 had PT's that increased over the course of the study, 2 had PT's that decreased over the course of the study, and 15 did not have a trend of increasing or decreasing (these were mostly up and down without a pattern). For the acamprosate arm, there were 7 whose PT pattern increased, 7 whose PT pattern decreased, and 23 whose PT pattern did not have a trend of increasing or decreasing (mostly up and down).

With regard to the degree of abnormality, there were 38 patients in Study 10 who had PT measurements which ranged from 120-150% of the upper limit of the normal range. No patient had a PT which was reported to be greater than 150% of the upper limit of the normal range and the abnormal results were, for the most part, distributed evenly throughout the abnormal range and between the two treatment arms.

Conclusion:

Laboratory information regarding the effects of acamprosate on coagulation was available for only two studies, the PRAMA and ADISE studies. Information was not provided with regard to the long term outcome (post-study) of patients who had an abnormal PT at the time of the last visit. In the PRAMA and ADISE studies, the patients treated with acamprosate were not significantly different from those treated with placebo in terms of the rate or severity of abnormal PT measurements. Although the study drug arm had a somewhat higher rate of patients with abnormal PT's for study 10, the pattern of PT elevation was not consistent with a

significant safety signal. Overall, based on this information, acamprosate does not appear to have an adverse effect on coagulation as measured by the prothrombin time (PT).

Analysis/Data Submitted by Sponsor

For evaluation of the effects of acamprosate on various other laboratory measurements, where possible, the medical officer reviewed analysis and summary tables submitted by the sponsor. This includes mean/median, min/max values at baseline and treatment phase endpoint; mean/median, min/max values for changes from baseline. Also included are shift tables which summarize end point values (low, normal, or high) for the total numbers patients who started with baseline values of either low, normal or high.

The sponsor's analysis examined the following groups: US 96.1 (U.S. short term study), pooled short-term European studies, pooled US 96.1 plus European short term studies, and pooled long terms studies as well as analysis of values pooled according to total daily dose pooled across studies. Also, data was presented for clinically significant laboratory abnormalities which occurred in clinical pharmacology studies, early clinical experience studies, and Phase IV studies.

Specific mention is provided for the review of the following laboratory measurements: uric acid, hematology, glucose, and liver function tests. The other laboratories provided by the sponsor were also reviewed and are mentioned in the "Other" laboratory review at the end of this section. There is also a section which contains the Medical Officer review of the sponsor's submitted analysis for laboratories of clinical significance.

The analysis and tables described in this review are located in Section 8.8 in Volumes 1.068 and 1.069 of the NDA.

Uric Acid

Based on a review of this data, there is no evidence to suggest that acamprosate has a significant deleterious effect on serum uric acid levels. There was no significant difference in uric acid measurements between study drug treatment arms and placebo arms, and no significant dose effect could be discerned amongst treatment arms with varying acamprosate doses.

Hematology

The specific hematological parameters which were reported include: hemoglobin, hematocrit, red blood cells, MCV, MCH, MCHC, white blood cells, neutrophils, lymphocytes, monocytes, basophils, eosinophils, and platelet counts.

Based on a review of this data, there is no evidence to suggest that acamprosate has a significant deleterious effect on the measured hematological parameters. For these parameters, there was no significant difference between study drug treatment arms and placebo arms, and no significant dose effect could be discerned amongst treatment arms with regard to varying acamprosate doses.

Because of specific SAE/deaths involving bleeding, the potential effect of acamprosate on platelet counts was considered. The analysis and summary tabulations supplied by the sponsor revealed no significant effect of acamprosate on platelet counts when compared to placebo. The most significant effect that could be found was in the analysis which examined the changes in platelet counts from baseline to endpoint in the safety population of the controlled long-term European studies (pooled). In this analysis, platelet counts in the patients treated with acamprosate fell from baseline by a mean of 8.1 percentage points relative to the upper limit of normal. (Table 8.8.10.9.0) However, overall, this did not result in a clinically significant decline as platelet counts were still within the normal range. In addition, the patients in the placebo arm experienced, on average, a decline in platelet counts of 8.5 percentage points relative to the upper limit of normal.

Glucose

Based on a review of the submitted data, there is no evidence to suggest that acamprosate has a significant effect on the measured blood glucose. There was no significant difference between study drug treatment arms and placebo arms, and no significant dose effect could be discerned amongst treatment arms with regard to varying acamprosate doses.

Liver Function Tests

Submitted data was reviewed for the following liver function tests: AST, ALT, bilirubin, alkaline phosphatase, GGT, LDH, and albumin. (tables/analysis describing shifts from baseline for LDH and albumin were not submitted by the sponsor)

There was no significant deleterious effect of acamprosate on LFT measurements based on the information submitted by the sponsor. The rates of patients who had baseline normal or abnormal LFT measurements were similar between acamprosate arms and placebo. The rates of patients whose LFT's became elevated during the study (from a baseline of normal) as well as the rates of patients whose LFT's became normal (from a baseline of elevated) were similar between the acamprosate arms and placebo. This was true for both the long term and short term studies and the U.S. study.

It is interesting to note that there were significant numbers of patients in the acamprosate and placebo treated arms who had baseline elevations of AST, ALT, and GGT. (Tables 8.8.10.5.0, 8.8.10.6.0, 8.8.10.7.0, 8.8.10.11.0) This degree of elevation is consistent with alcoholic hepatitis. Significant percentages (general range of 20-50%) of these elevated LFT's returned to normal during the course of the trial which is consistent with cessation of alcohol consumption. (Tables 8.8.10.5.0, 8.8.10.6.0, 8.8.10.7.0, 8.8.10.11.0) The rates of return to normal LFT values were generally very similar between the placebo arms and the acamprosate arms suggesting that in addition to acamprosate treated patients, placebo treated patients also had reductions or cessation of alcohol consumption.

Creatinine

Although the pre-clinical animal studies suggested potential for renal toxicity, the data submitted in this NDA are not consistent with renal toxicity in humans. There was no

significant difference between study drug treatment arms and placebo arms, and no significant dose effect could be discerned amongst treatment arms with regard to varying acamprosate doses.

Other Laboratories

Other laboratories were evaluated including electrolytes (sodium, chloride, potassium, calcium, phosphorus), urinalysis, blood urea nitrogen. Review of the submitted data reveals no effect of acamprosate on these laboratories.

Clinically Significant Laboratories

The following laboratory parameters were analyzed with regard to incidence of post-baseline clinically significant laboratory abnormalities: hematologies, renal function laboratories, electrolytes, urine protein/glucose/casts, and LFT's. These were measured for the following controlled short term studies: US 96.1, PELC II, ADISA, and TEMPESTA , - other short term studies did not monitor for clinical significant laboratories. For controlled long term studies PRAMA and PAILLE were the only studies to measure clinically significant laboratories (and PAILLE did not measure all of the above listed parameters).

With regard to post-baseline clinically significant AST measurements, there was a higher rate in the ACAMP pooled group (7% or 26/393) than there was in the placebo group (3% or 7/238). However, this difference probably represents a spurious finding because all other potential corroborating laboratories (ALT, GGT, total Bili, alkaline phosphatase, hemoglobin, hematocrit) did not reveal a difference between the two treatment arms in the incidence of post-baseline clinically significant measurements.

Examination of the potassium measurements of post-baseline clinical significance revealed no difference in incidence for the short-term studies which measured potassium. PRAMA was the only long-term study which measured potassium. The incidence of post-baseline clinically significant potassium measurements in the controlled long-term study, PRAMA, was different between the ACAMP pooled arm (15% or 17/114) and the placebo arm (8% or 9/109). (TABLE 8.8.10.12.2) Such a difference was not apparent when examining the clinically significant laboratory abnormalities for the short-term studies. Also, the analysis for PRAMA of potassium mean/median, min/max and changes from baseline did not reveal any significant findings, however, this form of central tendency analysis is not particularly sensitive to potential changes which may actually exist in individual patients or subsets of patients. Further review of data submitted by the sponsor on 5/21/02 addresses this issue of elevated potassium measurements in the PRAMA study. According to this information, the majority of the elevated measurements were the result of either laboratory error or hemolysis.

There were no other significant differences between the acamprosate treatment arms and placebo with regard to the incidence of clinically significant laboratory abnormalities.

Clinical Pharmacology Studies/ Early Clinical Experience Studies

Hematology, clinical chemistry, and urinalyses tests were performed at Baseline and at post-treatment study visits as indicated by each study protocol. Laboratory tests and study visits

were not standardized across studies, nor were clinical laboratory assessments performed in all studies. Clinically significant laboratory abnormalities were identified and summarized directly from the study reports. If the study report was unclear regarding clinical significance of clinical laboratory findings, the laboratory listings were compared to the normal ranges for each study, if available. Values in the laboratory listings that were above or below the normal ranges as defined in each study were then evaluated based on the clinically significant criteria provided in In-Text Table 8.8.9:1.

A summary of clinically significant laboratory abnormalities for the completed clinical pharmacology studies is presented in In-Text Tables 8.8.9.4:1 and 8.8.9:1 .

Medical Officer review of these tables did not reveal laboratory results consistent with a significant safety signal. No clinically significant hematological, clinical chemistry, or urinalysis laboratory abnormalities were noted in any of the 4 early clinical experience studies that reported laboratory assessment results. A total of 714 patients were enrolled in the 4 early clinical studies reporting laboratory assessment results.

Phase IV Studies

The incidence of clinically significant clinical laboratory parameters that occurred in the the NEAT studies conducted in Belgium (1 main study and the extension of that study), Switzerland, Austria, United Kingdom, and Portugal, are summarized in In-Text Table 8.8.9.6:1. A listing of clinically significant laboratory parameters in the NEAT studies by study is presented in Appendix 8.8.21:14. The incidence of clinically significant clinical laboratory parameters that occurred in the Ades study is summarized in In-Text Table 8.8.9.6:2. The incidence of clinically significant clinical laboratory parameters that occurred in the MERAM Phase IV study conducted in France, the ASATIM study conducted in France, and the Integral study conducted in Germany, are summarized textually. All studies were open-label with a 6-month acamprostate treatment period with the exception of the MERAM Phase IV study, which had a 3-month treatment period; the ASATIM study, which had a 15-day treatment period with co-administration of Atrium, Equanil, or Seresta; and the Ades study, which had a 2-month treatment period.

The clinically significant laboratory parameters listed in In-Text Table 8.8.9.6:1 were included if a patient had one or more assessment which was considered to be significantly different from the normal range according to the assessment of the treating physician. The clinically significant abnormal values were categorized into classes of possible causality: cause only related to alcohol, cause only related to non-alcohol conditions, and causes where both alcohol and other causes combined could have contributed. A clinically significant laboratory parameter could be identified more than once for a single patient. Among the 1,230 patients in the 5 NEAT studies with clinical laboratory data, a total of 306 clinically significant laboratory parameters were reported. The majority of abnormalities were directly attributed to alcohol (259 abnormalities). Clinically significant laboratory abnormalities were reported most frequently for GGT, MCV, ALAT, and ASAT. Only 1 patient had a clinically significant laboratory parameter that was attributed to study medication (serum calcium). None of the clinically significant laboratory parameters were considered to be a SAE.

In the Ades study, a total of 43 patients had a total of 66 abnormal biological values at the end of the study that according to the investigators had clinical relevance. The majority of these clinically significant abnormalities were considered by the investigator related to the patients' alcoholism. None of the clinically significant laboratory parameters were considered to be a SAE.

There were no clinically significant laboratory parameters reported for the MERAM Phase IV study. In the Integral study, 1 patient was hospitalized for a diagnostic procedure (pathological blood electrophoresis) that was performed during the study period. The relationship between this event and study medication was considered as not assessable and the patient was not withdrawn from treatment. No other clinically relevant abnormality of laboratory parameters was considered a SAE. The majority of significant abnormalities of laboratory parameters at the end of the treatment period were thought to be caused by alcohol intake and respiratory infections. No clinically relevant laboratory abnormality parameters were considered as causally related to study medication in the Integral study.

In the ASATIM study, there were 2 cases of thrombocytopenia requiring withdrawal from the study. These cases were reported to be associated with the patients medical conditions and not study medication. Statistically significant differences between clinical laboratory values at baseline and Day 15 (end of study) for each treatment group were reported as unlikely to be clinically significant.

In these clinical pharmacology, early clinical, and Phase IV Studies, there is no placebo arm and there is no control with a known adverse event profile. Therefore, it is difficult to determine the significance of the reported abnormal laboratory values. For the most part, these abnormal values, are consistent with the underlying disease of alcoholism, and therefore, it is not possible to attribute such laboratory abnormalities to the drug.

Conclusion:

Medical Officer review of the submitted data does not indicate that there is a significant effect of acamprosate on any of the laboratory parameters measured during the pharmacokinetic, pre-clinical, and controlled clinical acamprosate studies.

VITAL SIGNS

Vital signs (including systolic/diastolic blood pressure, heart rate, and body weight) and changes in baseline were measured and analyzed for the following studies: (short term) U.S. 96.1, PELC II, and (long term) PRAMA, PAILLE. (TABLES: 8.8.11.0.1, 8.8.11.0.2, 8.8.11.0.3, 8.8.11.1.0, 8.8.11.1.1, 8.8.11.1.2, 8.8.11.1.3, 8.8.11.2.0).

There were no significant differences between treatment arms and placebo with regard to the mean/median/changes from baseline or incidence of clinically significant laboratory abnormalities.

ECG's

Pre-clinical Studies

The sponsor did perform animal studies regarding the effects of acamprosate on cardiac electrophysiology. These pre-clinical studies were reviewed by the FDA Pharmacology/Toxicologist on the Acamprosate review team.

- A safety pharmacology study was performed to assess CV effects in anesthetized dogs. Slight increases in PR and QRS interval were noted at all doses (30-1000 mg/kg, IV) but there do not appear to be any effects on QT interval.
- In a 6-month dog study, the high dose group (1000 mg/kg) demonstrated one 2nd degree auriculo-ventricular heart block 90 min after the first dose, one 1st degree block before administration in week 13 in one male, one ventricular premature beat at lead II before administration in week 13 in another male, and several 2nd degree auriculo-ventricular blocks before administration in week 13 in one female. Of note, one 2nd degree auriculo-ventricular block was observed at baseline in 1 control female. This study did include assessment of QT interval with no changes noted.
- ECG was not assessed in rats.

ECG Results for Clinical Pharmacology, Early Clinical Experience, and Phase IV Studies

Electrocardiogram results are summarized for 17 clinical pharmacology studies that reported post-Baseline ECG data in Appendix 8.8.21:19. In 16 of the 33 completed clinical pharmacology studies, ECG recordings were either not performed or only performed at the start of the study.

No clinically significant changes in ECG recordings were reported for any of the 296 subjects in the 17 clinical pharmacology studies that reported post-Baseline EC results.

There were no post-Baseline ECG results reported for any of the 6 early clinical experience studies.

No ECG assessments were performed in the Phase IV studies.

Phase III Studies

Only two phase III studies routinely measured ECG's as part of the study protocol. These studies include the two short-term studies, US 96.1 and UKMAS.

No long-term studies performed ECG's.

US 96.1

Electrocardiogram recordings were performed at Baseline and at end of treatment evaluation in the US 96.1 study. Table 8.8.12.0.0 summarizes the incidence of ECG abnormalities at Baseline and Endpoint by treatment group.

The percentage of patients with abnormal, but acceptable ECGs at Baseline was similar among the 3 treatment groups: acamprosate 1998/2000 mg/day, 76 patients (30%); acamprosate 3000 mg/day, 29 patients (35%); and placebo, 83 patients (32%). The sponsor did not indicate a definition for ECG's which were considered to be "abnormal but acceptable." The percentage of patients with treatment-emergent ECG abnormalities was also similar among the 3 groups: acamprosate 1998/2000 mg/day, 10 patients (6%); acamprosate 3000 mg/day, 5 patients (9%); and placebo, 10 patients (6%). Overall, the changes noted were of a nonspecific variety as reported by the sponsor.

UKMAS

Electrocardiogram recordings were performed at Baseline, Visit 7 and at Endpoint (Visit 10) in the UKMAS study. The incidence of ECG abnormalities at Baseline and Endpoint, and shifts in ECG results from Baseline to Endpoint, are summarized in Appendix 8.8.21:17 and Appendix 8.8.21:18, respectively.

The percentage of patients with abnormal ECG results at Baseline was similar between the 2 treatment groups (acamprosate 1998/2000 mg/day: 110 patients 39%; placebo, 128 patients, 44%). The percentage of patients with abnormal ECG results at Endpoint was also similar between treatment groups (acamprosate 1998/2000 mg/day: 55 patients 38%; placebo, 57 patients, 37%). Furthermore, the percentage of patients with a shift in ECG results from normal at Baseline to abnormal at Endpoint was similar between treatment groups (acamprosate 1998/2000 mg/day: 26 patients, 18%; placebo, 22 patients, 14%). A similar percentage of patients in the acamprosate groups, and a slightly greater percentage of patients in the placebo group, had a shift in ECG results from abnormal at Baseline to normal at Endpoint (acamprosate 1998/2000 mg/day: 30 patients, 21%; placebo, 35 patients, 23%) compared with the percentage of patients with shift from normal at Baseline to abnormal at Endpoint.

The sponsor did not submit information or data which describes in detail, the types of abnormal ECG's which occurred during these studies. For this reason, a more complete assessment of the potential effects of acamprosate on cardiac electrophysiology is difficult to complete based on this information alone. Individual patient data for those patients with abnormal ECG changes from Baseline are listed in Table 8.8.12.1.0, however, this listing does not appear to include all of those patients in Table 8.8.12.0.0 who were categorized as "other". For these reasons, the sponsor was requested to submit further information. A more detailed review of the changes which were categorized as "other" was performed after further information was submitted by the sponsor on 5/21/02. This additional information included a detailed listing describing these changes. There were no specific safety concerns identified from review of this additional data. There were two patients with prolonged QT intervals at study endpoint (11R006 and 14R004) but these patients did not have baseline ECG's performed and only one of them was treated with acamprosate (the other was treated with placebo). There was one additional patient whose baseline ECG was characterized as "borderline QT." No baseline ECG was obtained for this patient.

Supplemental Information

ECG Intervals

A supplement was submitted by the sponsor on March 20, 2002 (Amendment #009) in response to a request by the division for further ECG information. As part of the amendment, the sponsor did submit analysis detailing the statistics of central tendency (mean, median, min, max, standard error, and changes from baseline) by age, gender, and overall for the following ECG parameters: QTC, ventricular rate, QT interval, PR interval, QRS interval. Also submitted in this amendment were tables which summarized the post-baseline interpretations for QTC as separated into three categories: normal, borderline, or prolonged. MO review of this analysis did not reveal any significant differences between the treatment arm and the placebo arm.

Also submitted in this amendment were line listings of all individual patients in both the US96.1 and UKMAS studies. These line listing provide detailed information for each patient with regard to QT/QTC and P-R intervals. For US96.1, data on QRS duration was also provided. An analysis of this data was performed by the medical officer. There were no differences between the two arms in the incidence of significant QT changes defined as one or both of the following: 1) QTC change from baseline of > 60 milliseconds or increase of >15% ; 2) QTC>440 and % change from baseline of >10). In the US 96.1 study, there were 5 patients in the acamprosate arm and 6 patients in the placebo arm who experienced one or both of those QT changes. In the UKMAS study, there were 13 patients in the acamprosate arm and 14 patients in the US96.1 arm who experienced one or both of these QT changes.

Analysis was performed by the Medical Officer to assess the potential effects of acamprosate on A-V nodal conduction. This was done by comparing the numbers and degree of severity of P-R interval prolongation between the study drug and placebo. Based on this analysis, there does not appear to be a significant difference between acamprosate and placebo with regards to the effect on the P-R interval.

The following table details the results of the medical officer analysis of P-R intervals for the two studies.

Number of Patients with Increases in P-R Interval by Milliseconds								
Study	Acamprosate				Placebo			
	20ms	21-39ms	40ms	>40ms	20ms	21-39ms	40ms	>40ms
UKMAS	18	1	15	1	25	2	11	0
US96.1	8	10	1	1	8	5	1	1
Total	55				53			

The submitted data included listings of the QRS intervals for patients in study US96.1 but not for the UKMAS study. A Medical Officer analysis of this data did not identify any significant differences between the study drug and placebo with regards to effect on QRS duration. There were more patients in the Acamprosate arm who had QRS duration increase of between 11-15 ms. The significance of this is unclear given that all other interval increases were identical between the two treatment arms. Increases in QRS duration beginning with 6 milliseconds were assessed because any increase of 6 milliseconds would ensure a shift from a normal QRS duration to an abnormal one.

The medical officer analysis of this data is presented in the table below.

Number of Patients with Increases in QRS Interval by Milliseconds								
Study	Acamprosate				Placebo			
	6-10 ms	11-15 ms	16-20ms	>20 ms	6-10 ms	11-15 ms	16-20 ms	>20 ms
US96.1	8	10	1	1	8	5	1	1
Total	20				15			

Conclusion:

Based on the information provided, it does not appear that acamprosate has any significant effect on the P-R or QRS intervals when compared to placebo.

It should be noted, however, that no ion channel studies were performed. These types of studies (i.e., IKR studies, HERG studies) are currently recommended for first-in-class type new drugs, NME's), but were probably not done because drug development for this product occurred 10-15 years ago.

The data presented by the sponsor on ECG's performed during this clinical trial were obtained from machine read ECG's. At the present time, it is the standard recommendation that blinded manual readings by cardiologists be done to assess the QT interval. This may be particularly important for NDA's in which there is a suspicion of possible drug effect on cardiac repolarization or for those NDA's for which prior class experience is lacking (NME's). In the case of acamprosate, there is no pre-clinical data to suggest that it has a deleterious effect on repolarization, however, it is a new molecular entity for which electrocardiologic and ion channel pre-clinical data are incomplete. For this reason, it makes sense to recommend manual readings as performed by blinded cardiologists to affirm the initial impression that this drug does not effect the QT interval. It would be impractical and difficult to perform such a task for all ECG's performed in phase III clinical trials (UKMAS and US96.1). An alternative approach which may provide even more useful information would be to perform blinded manual ECG readings by a cardiologist only for the specific dose escalating pharmacokinetic studies which were performed in phase I. The effects of differing doses (which increase to a final fairly high dosage) in otherwise healthy participants would most likely provide sufficient complimentary

data which may then allow a more confident conclusion. For this reason, it is recommended that the sponsor perform manual ECG readings with blinded cardiologists for the following studies: Dewland I (n=18), Dewland II (n=6), Theodor II (n=62), and Jaillon (n=12).

OVERDOSAGE INFORMATION

Summary of Data

Information regarding overdose was supplied by the sponsor in section 8.9. This information was reviewed by the Medical officer and contained a summary of all 21 cases of reported acamprosate overdoses as obtained from the Corporate Drug Safety Department of Lipha, and from a tri-monthly literature search of electronically-available medical databases (MEDLINE, EMBASE, BIOSIS, PASCAL, DERWENT, and SCISEARCH).

Information supplied by the sponsor is contained in the Table 8.9.2:1. All but one of the overdoses were intentional and involved suicide attempts in which other drugs and/or alcohol was consumed. The range of overdose was from 4.33 to 56gr of acomprosate (13-168 x 333mg tablets).

6 of the 21 cases contain no outcome data, and of the remaining 15 cases, 3 patients died and 12 recovered. Also, there were 4 patients for whom the only reported fact was that an acamprosate overdose occurred.

There were no overdoses in which acamprosate was the only drug/substance ingested. Most of the cases involved at least one or more additional other drugs such as anti-depressants, benzodiazepines, acetomenophen, phenobarbital, aspirin, phenothiazines, and alcohol. There were 4 patients who took overdoses of acamprosate with alcohol but no other concomitant medications, 2 experienced syncopal reactions of which one did not have outcome data reported and the other (presumably) recovered. Of the other two, one had transient diarrhea and the other was asymptomatic and was treated with gastric lavage.

Acamprosate is a calcium salt (33mg calcium per 333mg tablet), and therefore, serum calcium levels were measured in 3 cases in which total acamprosate ingestion was 30gr, 28 gr, and 26.6 gr. In all three cases, serum calcium levels were normal.

Reported adverse events reported to have occurred in patients with acamprosate overdose include: syncope (n=2), gastrointestinal symptoms (n=3), agitation (n=2), somnolence (n=2), cardiac arrest (n=1).

There were a total of 3 deaths:

- **Case 1500033** had overdosed on both paroxetine and acamprosate. The patient had pyrexia, seizures, and cardiac arrest. After a period of stability and improvement, there was another cardiac arrest. Autopsy findings suggested that death was due to alcohol withdrawal syndrome.

- **Case 1500090** was found dead, and overdose was suspected. In addition to acamprosate, the patient had been taking diazepam and chlomethiazole. No further information is available.
- **Case 1200374** was an intentional overdose of phenothiazines and acamprosate overdose was questioned. However, acamprosate blood level was within the therapeutic range and phenothiazine levels were very high. In addition, there was evidence of alcohol intoxication.

Interventions and testing which were administered to patients with acamprosate overdose include the following: emesis induction, activated charcoal administration, gastric lavage, and serum calcium assessment.

Proposed Package Insert Section Regarding Overdosage

The following is the passage in the proposed Package Insert addressing the issue of overdose:

In all reported cases of acute overdosage with BRANDNAME (total reported doses of up to 56 grams of acamprosate), the only symptom that could be reasonably associated with BRANDNAME was diarrhea. 1

Conclusion:

Because these patients ingested other substances such as other drugs and/or alcohol, it is difficult to determine the causality of acamprosate for the specific adverse events which occurred in the individual cases of overdose. It is possible that acamprosate and/or the calcium contained in acamprosate tablets were at least partially responsible for some of the various adverse events which occurred in the patients with acamprosate overdose. However, evaluation of the available information did not identify a definite safety signal with regard to acamprosate overdose.

POSTMARKETING INFORMATION

Post-marketing adverse drug reactions (ADRs) for acamprosate were collected from September 1, 1989 through July 31, 2001. Individual pharmacovigilance reports summarizing ADR data reported during this reference period are included in Appendix 8.8.21:21a. A listing of all serious unexpected and non-serious unexpected ADRs is presented in Appendix 8.8.21:21b.

Adverse drug reactions included in the reports are those received from worldwide sources by the Corporate Drug Safety Department Liphia s.a. and stored in the Drug Safety Monitoring Database. Not included are medically unsubstantiated consumer reports that were not considered medically significant. The reports also include ADRs identified in literature searches of medical databases (MEDLINE, EMBASE, BIOSIS, PASCAL, DERWENT, and SCISEARCH) that were conducted every 3 months using the search criteria acamprosate.

It is estimated by the sponsor that τ 1 patients have been treated with acamprosate since market introduction. Such estimates serve as a best estimate but are often significantly inaccurate. In the case of this drug, there are the following problems with such a calculation: there is a long treatment duration; this patient population has known problems with compliance; single patients may receive successive courses of treatment which may then be counted as multiple patients. Therefore, when combined with under-reporting that is typically found in post-marketing passive AE reporting systems, it is very difficult to generate an accurate idea of the rates of various AE's reported in the post-marketing phase.

Although no definitive causal relationship to acamprosate has been proven, the following AEs have been reported to be temporally associated with acamprosate treatment in at least 3 patients (unless otherwise noted). Concomitant medications and alcohol withdrawal or relapse are confounding factors in the interpretation of many of these events. Acute renal failure (n=3), auditory hallucinations, bullous dermatitis (n=3), confusion, dizziness epileptiform attack, headache, hepatitis, hypersensitivity syndrome (n=4, all in association with Atrium®), hyponatremia, hypotension, increased liver enzymes' overdose, paranoid psychosis, photosensitivity, suicide attempt, and urticaria.

The following information was generated by Medical Officer review of Volume 1.072 of the NDA.

The sponsor provided listings and selected brief descriptions of all post-marketing reports of adverse event from February 1989 through July 2001. The adverse events occurring during the initial 6 years were compiled by the then license holder, Meram Laboratories, during which time, acamprosate was only available in France. After the European launch date for this product, regular safety update reports summarizing post-marketing safety information were submitted to European regulatory authorities. These updates comprise the majority of the post-marketing safety data submitted for January 1995 to July 2001.

Medical Officer review revealed multiple reports of adverse events which might be attributable to the underlying illness of alcoholism. These include the following: hallucinations, psychosis, suicide attempts, somnolence, depression, confusion, peripheral neuropathy, dizziness/ataxia, pancreatitis, hepatitis, gout, and neutropenia. The potential impact of acamprosate on these adverse events is difficult to determine from this type of data and review of the adverse events of the placebo controlled trials should provide a more accurate assessment.

There were, however, some reported adverse events which were not easily associated with the underlying disease. Although, these were most often very few in number, they could represent potential associations to the study medication.

Galactorrhea/Gynecomastia/Hyperprolactinemia

There were 5 patients who had one or more of the following: gynecomastia, galactorrhea, hyperprolactinemia. There are few other details about these cases and no mention of other

possible causes such as concomitant medications. This is an AE of special interest because of possible biologic plausibility. Makinen M et al reported in *J Neural Transm Gen Sect* (1993;94(3):155-63) that homotaurine was capable of stimulating significant increases in serum prolactin levels in an experimental rat model and theorized that homotaurine may cause the inhibition of dopamine release from the median eminence, thus causing increased prolactin secretion. The sponsor submitted a reference (*J Clin Psychopharmacol* 1999 Aug;19(4):387-9) entitled "Lack of effects of acamprosate on anterior pituitary secretion in healthy subjects." However, the article itself was not submitted for review and therefore, it was not assessed with regards to such potentially relevant issues as the dosing used in the study and the duration of treatment.

Dermatologic Adverse Events

Of interest, there were several AE's reported which were skin related. One such AE was erythema multiforme. In the post-marketing experience, there has been four reports of erythema multiforme. One case of erythema multiforme was reported in *Lancet* (Fortier-Beaulieu M, et al. *Lancet*, 1996 Oct 3;340(8823):856-7). This case was contested in a response letter also published in *Lancet* in which it is pointed out that the patient had a recent herpes infection and also that the biopsy may actually have been more consistent with interface dermatitis. This argument may not be accurate since the standard Dermatology text by Fitzpatrick states that interface dermatitis is a common component of erythema multiforme. There was one death due to Stevens-Johnson Syndrome (erythema multiforme major). This patient was on concomitant medications at the time including the following: troxerutine and atrium (febarbamate, defebarbamate, phenobarbitol). However, the sponsor did not clarify the presence or lack of a temporal relationship of these concomitant medications with the onset of the AE. The third case was a patient who was hospitalized because of severe rash and oral mucosal lesions which sounds suspicious for erythema multiforme. This patient had begun treatment with acamprosate and Atrium three days prior to the AE. The fourth case was a 40 year old male who was biopsy diagnosed with "toxicodermia" reported as being closely related to erythema multiforme (which was listed reaction description). This patient appears to have also been on Atrium as well.

Other skin-related AE's include 4 reported cases of bullous dermatitis. One of these occurred in a patient 6 weeks after beginning therapy with both Atrium and acamprosate and resolved after discontinuation of both. One patient was a 39 year old with an AE suspicious for erythema multiforme developed a "bullous eruption" with "target lesions" which occurred 4 days after acamprosate was initiated. Such a description is consistent with erythema multiforme. One patient developed bullous skin lesions after a few weeks of therapy with acamprosate while being concomitantly treated with quetiapride and venflaxine. The skin lesions resolved after stopping *only* the acamprosate. The fourth patient experienced facial edema, itching rash, and single bullous eruption after one day of therapy with acamprosate. The patient was also taking vitamin B complex but the rash disappeared after stopping *only* the acamprosate.

There were also >15 cases of erythematous rashes, and 6 non-serious cases of photosensitivity. There was also a single report of plantar desquamation which began 14 days after starting therapy. The symptoms resolved after stopping the acamprosate.

Cardiac Adverse Events

Other AE's of interest include 3 cases of hypertension (one with a positive rechallange), 5 cases of hypotension two of which were prolonged and only resolved with acamprosate discontinuation, and 3 cases of aggravated angina pectoris, two of which had positive re-challenges.

Renal Adverse Events

Because of pre-clinical studies which identified potential renal toxicity of acamprosate, post-marketing data was evaluated for cases of renal failure. The revealed three cases of acute renal failure. One was in a 51 year old who had taken an overdose of acamprosate and was diagnosed on biopsy with acute tubular necrosis. The second other was in a 35 year old who had been experiencing nausea, vomiting, and diarrhea. Renal biopsy revealed interstitial nephritis which subsequently resolved 10 days later while the patient remained off acamprosate. The third case occurred in a patient after 10 days of therapy with acamprosate. No further information on this patient was available for review. In addition, in Switzerland, there was one reported case of glomerulonephritis/ glomerulosclerosis (unclear which one it is) without any further detail.

Hypersensitivity Hepatitis

There were three cases of hypereosinophilia, hepatitis, and rash reported. All three were taking Atrium which contains phenobarbital which has been reported to produce this kind of hypersensitivity reaction. Only one of the three specifies what the chronology was with regard to the medications. In that patient, both the Atrium and acamprosate were started at the same time. For the other two, the chronology is not clear, however, there appears to be a temporal relationship with acamprosate.

Serum Sodium/SIADH

There were pre-clinical animal data which found that acamprosate caused some degree of hyponatremia. For this reason, the post-marketing data was examined for reports of hyponatremia. There were five reported cases of hyponatremia or SIADH. Two of these patients were also taking fluoxetine which is known to be associated with SIADH. One case occurred on a patient 3 months after the start of acamprosate and lorazepam. The patient had been on maprotiline and zolpidem for 2.5 years. The hyponatremia improved after stopping all medications. One patient experienced hyponatremia in the context of a paranoid psychiatric illness. Concomitant medications for this patient included Atrium and tiapride. The hyponatremia resolved after discontinuation of the Atrium and acamprosate. The fifth patient was speculated to have had polydypsia (2-3 L/day) as the cause of his hyponatremia, although the problem resolved after cessation of the acamprosate.

Unusual Reported Adverse Events

There were specific unusual single reported adverse events in the post-marketing data. These include the following: ulcerative colitis (a study patient), and central pontine myelinolysis, and a single case of tetany (with a positive rechallenge). Also, there was one case of rhabdomyolysis (CK=5,000UI) after one month's therapy, however, CK's in this patient later found to be normal only 2 days after acamprosate had been stopped which lead the sponsor to conclude that the potential association was doubtful. There was one case of Torsades de Pointes/cardiac arrest in a 37 year old after one month of therapy. However, this patient was hypokalemic due to diarrhea/nausea and later presented with hypokalemia and "ECG" abnormalities while not on acamprosate. He also had presented a few years earlier with hypokalemia and an enlarged QT interval.

Post-marketing and Pregnancy experience

With regard to pregnancies, there were a total of 28 pregnancies reported in patients who were taking acamprosate. Thirteen of these gave birth to normal children, five pregnancies have an unknown outcome, and five patients had elective abortions, two had fetal malformations, for three the outcome is not known.

Non-normal outcomes:

- One patient had an elective abortion at week 19 because of multiple fetal malformations which included: cleft palate, small excrecence of the caudal pole and dilatation of the fourth ventricle, growth retardation, and a normal karyotype. This fetal malformation was thought to be the result of fetal alcohol syndrome.
- One additional fetal malformation occurred which in which accidental acamprosate exposure occurred. In this case, the child died because of Edward's syndrome (trisomy 16-18).

Three additional cases of pregnancy with acamprosate exposure occurred in the period immediately preceding the lock-out date and the outcome was not known at the time of NDA submission.

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Deaths in the Post-Marketing Period

The following table summarizes all deaths reported in the post-marketing period.

AGE	Outcome	Reaction Description	Comment
49	Fatal	Stevens-Johnson Syndrome	Patient was started on troxerutine and atrium at same time as acamp. Sponsor assesses potential association as "dubious"
32	Fatal	Overdose suspected	No tox results. Patient also on diazepam, chlomethiazole
27	Fatal	Pulmonary Embolism	Patient had received only one day of treatment with acamprosate
56	Fatal	Sudden Death/ Cardiac Arrest	No further information provided
33	Fatal	Intentional Overdose	Tox analysis confirmed large doses of phenothiazines and alcohol. Acamp at therapeutic levels (does not say what level that is)
82	Fatal	Subdural Hematoma	Occurred after starting Acamp. Patient also on aspirin
39	Fatal	Sudden Death of unknown cause	Unknown treatment period/dose at time of death. Post mortem unrevealing.
?	Fatal	Sudden Death of unknown cause	No additional information. This was collected from NEAT study (Belgium)
?	Fatal	Sudden Death of unknown cause	No additional information. This was collected from NEAT study (Portugal)
?	Fatal	?	Reported in Sponsor's consumer ADR's from 1-August-2000 to 31-July-2001. No further information

Conclusion:

Because of the lack of a comparator, accurate usage data, and inefficiency in the passive AE reporting system that is usually used to detect post-marketing AE's, accurate information regarding causality and rates cannot be determined from this data. This data may be used to corroborate adverse event findings from the controlled clinical trials or provide information of possible associations for labeling purposes.

WITHDRAWALS DUE TO ADVERSE EVENTS

Conclusions:

With regard to assessing adverse events and withdrawals due to adverse events, serious adverse events, and deaths, the reviewing medical officer was unable to confirm the results presented in the ISS. Attempts were made to confirm the results presented in the ISS by examination of the submitted SAS transport datasets. However, review of these datasets raised many questions regarding the methodology and completeness of the analysis contained in the ISS.

For example, Medical Officer examination of the number of suicides, suicide attempts, suicide attempts by overdose, and depression with suicidal ideation revealed significant discrepancies between the Adverse Event Dataset, the patient narratives, and the ISS report. Attempts to reconcile these differences were unsuccessful.

Suggestions:

The following section contains specific recommendations for the sponsor which will allow FDA reviewers to more accurately and thoroughly review the submitted results.

- For Adverse Events, Serious Adverse Events, Deaths, and Withdrawals due to Adverse Events, all known and recorded events should be included in the analysis. The sponsor has used an arbitrary cut-off which excludes events which occurred 10 days post-treatment. In the current NDA submission, it is extremely difficult to characterize the adverse events which may have occurred following this 10 day cut-off. Characterizing such events is important for the following reasons:
 1. Acamprosate has a long half-life and therefore, 10 days may not be enough to capture AE's related to the use of this drug.
 2. Since it is postulated that this drug has an effect on the balance of various neurotransmitters, it would be of significant interest from a safety perspective to know what AE's (such as suicide, suicidal ideation, etc.) may have occurred upon withdrawal of the drug (i.e., after discontinuation).

All AE's, SAE's, and Deaths which were formerly categorized as having occurred in the "follow-up" phase, should be included in the safety analysis. This should include ALL known AE's for patients who participated in these clinical trials. It would be appropriate to include the following analyses: 1. an analysis of all such AE's separately in a "follow-up" analysis 2. an analysis of all AE's which occurred during "follow-up" combined with those occurring during "treatment phase" 3. AE's which only occurred during "treatment phase."

The inclusion of such an analysis (all AE's, SAE's, and Deaths which occurred during the "treatment phase" and "follow-up" phase) will allow the FDA the ability to account for ALL such events.

- The current NDA safety analysis cannot be confirmed by FDA reviewers because there is no clear variable in the adverse event data set indicating which AE's/ SAE's/Deaths/Dropouts due to AE's were included in the analysis and which were not. An ISS safety population variable does exist but it is not clear why many patients were not included in this population. A full detailed accounting of ALL AE's/SAE's/Deaths, and dropouts due to AE's should be included in the ISS.
- The adverse event dataset does not share with all the other datasets a unique identifying number for all patients. Therefore, FDA reviewers' attempts to merge various datasets are particularly difficult and are fraught with potential error. For this reason, the reviewers are obligated to confirm the veracity of each new dataset created from the merging of other data sets. This process is arduous and time consuming, and prevents an accurate and timely review of the data. Future submissions should assign a unique identifying number for each patient in the NDA and this should be included in all datasets such that merging of datasets can be done with some degree of accuracy. Attempts at merging datasets using multiple variables, including study number and patient ID have yielded results which do not match those reported in the NDA report.
- Narratives should be supplied for ALL patients who withdrew due to AE's, SAE's, and/or Deaths for ALL patients who participated in these studies. This includes ALL such events which occurred at any time (before, during, or after drug exposure). The present submission only includes narratives for those AE's/SAE's/Deaths/Dropouts due to AE's which were included in the sponsor's chosen analysis, but not ALL such events. The FDA would like to be able to account for ALL such events.
- In those situations where there is no recorded date of the adverse event, separate analyses should be conducted in which such AE's are included first in the on-therapy analysis, in the follow-up phase analysis, and in the combined analysis. When it is not clear as to whether a specific adverse event resulted in withdrawal from the study, it should be assumed that such adverse event did result in withdrawal from the study.
- There is conflicting information in this NDA as to how and when a particular AE was categorized as being a "Serious Adverse Event." For instance, in the data table of contents "define.pdf" which is included for the dataset SS_AES (adverse event dataset), there is a variable called "AESER." This variable is described in this file in the following way:

"Variable has a value of 1 to indicate if Adverse Event is Serious Adverse Event.
Note: primarily applicable to records from US 96.1 study. It should be mostly missing for records from the other 12 studies."

However, upon review of the adverse event dataset, it is evident that there are 71 adverse events from numerous studies other than US96.1 in which this variable is assigned. These studies include the following: Pelc II, Poldrugo, Lesch, Ladewig, Besson, Barrias. The majority of AE's for patients in these studies do not have an assignment for this variable. It is unclear why some, but not all AE's from these studies received a designation for this

variable. It appears that the decision to apply this variable is inconsistent and therefore, subject to bias.

In addition, for the study US96.1, there are listings for 686 adverse events which do not have an assignment for this variable. To further confuse this issue of the determination of serious adverse events, a description is included in the ISS which defines "Serious Adverse Event" determination in a completely different way. This definition is as follows:

"Serious adverse events were only identified in the database for the US 96.1 study. In order to identify an SAE according to the current FDA definition (i.e., an event which is fatal, life-threatening, results in or prolongs hospitalization, disability/incapacity, or a congenital anomaly/birth defect) and any event of cancer or overdose, a review of all study reports for the double-blind, placebo-controlled studies, was undertaken. Events meeting the FDA's criteria for an SAE were identified using subject narratives, descriptions of concurrent illnesses as reason for withdrawal, and AE listings. In addition, for studies with spontaneously reported AEs (US 96.1, UKMAS, ADISA, PRAMA, and Paille) SAEs were identified in the database by searching for the following terms or part of terms: hospitalization, hospital, surg, admit, inpatient, cancer, melanoma, carcinoma, suicide, and overdose."

It is not clear whether this described process resulted in the assignment of a result for the variable "AESER" or some other variable. It is also not clear why this methodology appears to have been only applied selectively.

- The datasets which were submitted by the sponsor are cluttered with large numbers of non-used variables and redundant variables which makes FDA review of the data difficult. The FDA reviewers need to be able to confirm the sponsor's reported results by examination of the datasets, and such verification is difficult with the present NDA's submitted datasets.

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/s/

Charles Cooper
6/11/02 01:34:54 PM
MEDICAL OFFICER

C.Cooper's Acamprosate safety review

Bob Rappaport
6/11/02 01:57:08 PM
MEDICAL OFFICER

I concur with Dr. Cooper's conclusions and recommendations

Cynthia McCormick
6/12/02 09:31:40 AM
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