

Table 7.5.1.3:1 Common Adverse Events in US 96.1:
Events Occurring At A Rate Of At Least 3% And Greater Than Placebo In Either Treatment

Group	Preferred Term	Acamprosate 2000 mg/day N = 258		Acamprosate 3000 mg/day N = 83		Placebo N = 260	
		N	%	N	%	N	%
BODY	ABDOMINAL PAIN	16	6%	4	5%	12	5%
	ACCIDENTAL INJURY*	19	7%	10	12%	26	10%
	ALLERGIC REACTION	3	1%	3	4%	6	2%
	ASTHENIA	11	4%	6	7%	13	5%
	FEVER	2	1%	3	4%	3	1%
	FLU SYNDROME	9	3%	7	8%	8	3%
	HEADACHE	49	19%	20	24%	60	23%
	LAB TEST ABNORMAL	8	3%	0	0%	3	1%
	VIRAL INFECTION	8	3%	0	0%	5	2%
	CV	HYPERTENSION	13	5%	2	2%	5
DIG	DIARRHEA	89	34%	33	40%	49	19%
	DYSPEPSIA	12	5%	7	8%	7	3%
	FLATULENCE	22	9%	4	5%	9	3%
	LIVER FUNCTION TESTS ABNORMAL	16	6%	4	5%	12	5%
	NAUSEA	13	5%	7	8%	15	6%
	VOMITING	11	4%	4	5%	3	1%
	HAL	MACROCYTIC ANEMIA	8	3%	4	5%	9
MAN	HYPERGLYCEMIA	10	4%	8	10%	12	5%
	HYPERURICEMIA	3	1%	3	4%	3	1%
NER	ANXIETY**	16	6%	6	7%	19	7%
	HYPERTONIA	6	2%	3	4%	1	0%
	ILLICIT SUBSTANCE USE	20	8%	4	5%	17	7%
	INSOMNIA	17	7%	9	11%	21	8%
	LIBIDO DECREASED	7	3%	4	5%	8	3%
	WITHDRAWAL SYNDROME	7	3%	2	2%	4	2%
SKIN	PRURITUS	14	5%	2	2%	10	4%

*includes events coded as "fracture" by sponsor **includes events coded as "nervousness" by sponsor
Table generated by reviewer from dataset SS_AES, selecting study = US 96.1, firstterm = 1.

In the overall safety dataset of studies in which spontaneous AEs were collected, a very similar list of most common terms emerged using the same criteria (events occurring at at least 3% in any treatment group, and more commonly than in the placebo group). However, for several terms, the rate of occurrence was higher in the U.S. study than in the overall database. For example, headache was reported by 19% of the 2000 mg/day group in the U.S. study, but the overall safety database shows that 11% of subjects in the combined 1998 mg/2000 mg group reported headache. Diarrhea was reported by 34% of the U.S. subjects in the 2000 mg/day group but by only 17% of the overall 1998 mg/2000 mg group in the broader safety database. Several terms are included in the list of overall safety experience exclusively because of data from the U.S. study. Again, this may be due to the closer monitoring of the U.S. study. However, because the 3000 mg/day group was included only

in the more closely-monitored study, evaluation of dose dependency is somewhat confounded. The table below illustrates the adverse event terms reported by at least 3% of subjects in any active treatment group where the event was more commonly reported in any active group than the placebo group. Events included solely on the basis of the experience in the 3000 mg/day group in the U.S. study are italicized. Events meeting criteria in the overall database but not in the U.S. database are highlighted.

Table 7.5.1.3:2 Common Adverse Events in Studies Collecting Spontaneously-Reported Adverse Events: Events Occurring At A Rate Of At Least 3% And Greater Than Placebo In Either Treatment Group

		Acamprosate 1332 mg/day N = 397		Acamprosate 1998/ 2000 mg/day N = 1539		Acamprosate 3000 mg/day N = 83		Placebo N = 1706	
		N	%	N	%	N	%	N	%
BODY	ACCIDENTAL INJURY*	20	5%	49	3%	10	12%	55	3%
	<i>ALLERGIC REACTION</i>	0	0%	6	0%	3	4%	10	1%
	ASTHENIA	29	7%	79	5%	6	7%	93	5%
	FEVER	2	1%	9	1%	3	4%	20	1%
	<i>FLU SYNDROME</i>	4	1%	32	2%	7	8%	24	1%
	HEADACHE	21	5%	172	11%	20	24%	187	11%
	INFECTION	3	1%	66	4%	14	17%	86	5%
DIGESTIVE									
	DIARRHEA	39	10%	257	17%	33	40%	166	10%
	DYSPEPSIA	1	0%	37	2%	7	8%	31	2%
	FLATULENCE	4	1%	55	4%	4	5%	28	2%
	LIVER FUNCTION TESTS ABNORMAL	0	0%	17	1%	4	5%	13	1%
	NAUSEA	11	3%	69	4%	7	8%	58	3%
	VOMITING	6	2%	52	3%	4	5%	48	3%
HAL	MACROCYTIC ANEMIA	0	0%	9	1%	4	5%	10	1%
MAN	HYPERGLYCEMIA	2	1%	10	1%	8	10%	12	1%
	HYPERURICEMIA	0	0%	4	0%	3	4%	3	0%
NERVOUS									
	ANXIETY**	37	9%	85	6%	13	16%	101	6%
	DEPRESSION	33	8%	120	8%	6	7%	87	5%
	DIZZINESS	15	4%	45	3%	3	4%	44	3%
	DRY MOUTH	5	1%	10	1%	0	0%	28	2%
NER	HYPERTONIA	0	0%	8	1%	3	4%	3	0%
	ILLICIT SUBSTANCE USE	0	0%	20	1%	4	5%	17	1%
	INSOMNIA	34	9%	94	6%	9	11%	121	7%
	LIBIDO DECREASED	11	3%	34	2%	4	5%	43	3%
RESPIRATORY									
	PHARYNGITIS	1	0%	11	1%	0	0%	32	2%
SKIN									
	PRURITUS	12	3%	68	4%	2	2%	58	3%
UNSPECIFIED									
	SWELLING	1	0%	1	0%	0	0%	3	0%

*Includes events coded as "fracture" **Includes events coded as "nervousness"

Table generated by reviewer from dataset SS_AES, selecting study = ADISA, Benelux, Poldrugo, Tempesta, UKMAS, US 96.1, Barrias, Besson, Paille, PRAMA, firstterm = 1.

Lipha also presented the data from short-term and long-term studies separately. In these data presentations, similar adverse event profiles are seen regardless of study grouping. Only diarrhea appears to be clearly more common among patients treated with acamprosate than those treated with placebo. Diarrhea was reported by approximately 20% of the acamprosate-treated subjects in short-term studies and 10% in long-term studies. Notably, the U.S. study had a much higher rate of reporting of diarrhea—34% in the 2000 mg/day group, 40% in the 3000 mg/day group, and 19% in the placebo group.

7.1.5.4 Severity of Common Adverse Events

Lipha tabulated the investigator-assigned severity of adverse events, where known, by body system in the studies with spontaneously-reported adverse events. The overall rate of occurrence of any particular term with a rating of “severe” was low. There was no term for which >4% of patients in the placebo, pooled acamprosate, or acamprosate 1998/2000 mg/day groups reported a “severe” event. However, comparing the number of patients reporting “severe” events to the total number reporting a particular term, it is apparent that a fairly substantial proportion of events were rated as severe. For example, for patients reporting diarrhea in the short-term studies with spontaneously-reported adverse events, 213 of 1108 patients in the **acamprosate 1998/2000 mg group** experienced diarrhea: for 50% (107 patients) the worst severity was “mild”, for 31% (67 patients) it was “moderate” and for 18% (39 patients) it was “severe”. In the **placebo group** 137 of 1186 patients experienced diarrhea: for 48% (61 patients) the worst severity was “mild”, for 40% (55 patients) it was “moderate” and for 15% (21 patients) it was “severe”. The distribution of severity was similar in the long-term studies. For some terms (e.g., insomnia), the worst severity was “severe” for as many as a third of the patients reporting the event. However, the distribution of severity was similar across treatment groups.

Other data presentations were provided to illustrate the results of adverse event collection by checklist. As noted above, five of the Group I Controlled Short-Term studies used worksheets as an aid to recording adverse events. However, 4 of the studies (**BENELUX, Pelc II, Poldrugo and Tempesta**) first recorded spontaneous adverse events on the worksheet, and then reviewed the worksheet with patients, thereby recording additional events. The spontaneously reported events from these studies were included in the tabulation of spontaneously recorded adverse events and were excluded from the tabulation of worksheet elicited events. If an event was spontaneously reported and the same event was also recorded after worksheet review, it was only considered to be a spontaneously reported event. Therefore, the dataset of worksheet-elicited events actually excludes patients who may have endorsed various symptoms included on the worksheet. For this reason, the rates of adverse event reports based on worksheet review does not appear to add useful information to the above analysis. Examination of the tabulated adverse events from worksheet review (Sponsor’s In-Text Table 8.8.7.1.5:1) reveals that only diarrhea was reported at a markedly higher rate in acamprosate-treated than placebo-treated patients (11%

vs 6% in short-term studies; 16% vs 7% in long-term studies). When the data for short-term and long-term studies were pooled, various terms were endorsed by more patients in the 1332 mg/day group than in the placebo group, but the experience in the 1998 mg/day group was similar to placebo. In the pooled acamprosate group, diarrhea was again the only term which occurred with a substantially greater frequency compared to placebo (14% acamprosate, pooled; 13% acamprosate 1998 mg/day; 7% placebo).

7.1.5.5 Incidence of Treatment-Emergent Adverse Events by Treatment Exposure

Lipha tabulated the incidence of treatment-emergent adverse events (TEAEs) as a function of treatment exposure for those Group I studies which consistently captured adverse event start and stop dates. These include:

	Acamprosate 1332	Acamprosate 1998/2000	Acamprosate 3000	Acamprosate pooled	Placebo
Controlled Short-Term Studies (3 of 8)					
ADISA	N/A	147	N/A	148	148
UKMAS	N/A	289	N/A	289	292
US 96.1	N/A	258	83	341	260
Total short-term	N/A	694	83	722	710
Controlled Long-Term (3 of 5)					
Barrias	48	102	N/A	150	152
Paille	188	173	N/A	361	177
PRAMA	24	112	N/A	136	136
Total long-term	260	387	N/A	647	465
TOTAL	260	1081	83	1415	1175

Treatment exposure categories were defined as: 0-<4 weeks, 4-<8 weeks, 8-<13 weeks, and ≥13 weeks for the Short-Term studies (planned duration 26 weeks or less), and 0-<4 weeks, 4-<8 weeks, 8-<13 weeks, 13-<26 weeks, 26-<39 weeks, and ≥39 weeks for the Long-Term studies (planned duration 48 weeks to 52 weeks). Events are counted in each time interval during which they started. Patients are counted at most once within each COSTART body system, COSTART adverse event preferred term, and time interval. Patients are counted in the denominator if they were present during the time interval. Events with missing start dates are not included.

There was no evidence of the overall rate of adverse events increasing as a function of time on active treatment for any of the acamprosate treatment groups. Selected terms were examined for time-dependency and some were clearly more common during the first four weeks of treatment. However, this pattern was also apparent for discontinuations due to adverse events. Therefore, the lower rate of adverse events after the first four weeks of treatment could be explained either by transience of the symptoms, or by treatment discontinuation by patients experiencing those symptoms.

7.1.5.6 Adverse Events in Non-Group I Studies

The overall profile of adverse events from non-Group I studies where adverse events were collected was tabulated and described by Lipha. The terms reported and incidence rates were consistent with the data from the Group I studies.

7.1.6 Laboratory Findings

7.1.6.1 Extent of Laboratory Testing in the Development Program

The extent of laboratory testing varied across the studies in the development program. Furthermore, laboratory results were reported using various local standards, including different units and different normal ranges. For many analyses, values normalized to the upper limit of normal (ULN) for the local laboratory were used. Actual observed values were reported in dataset SS_LABAN for only 6 studies: ADISA, PRAMA, Paille, Pelc-II, Tempesta, and US 96.1.

7.1.6.2 Hematology

Alcoholism has many adverse effects on hematologic parameters. Direct toxic effects on bone marrow as well as the effects of alcoholism-associated malnutrition and other deleterious effects of alcohol on blood cells combine to create a high prevalence of hematologic abnormalities in the alcoholic population. Therefore, it is difficult to tease out possible effects of acamprosate in the context of the effects of alcohol.

The following hematology parameters were measured during the Group I short-term studies. No study appears to have collected information on coagulation parameters, well known to be abnormal in the alcoholic population:

Hematologic Assessments in Group I Studies

	ADISA	BENELUX	Ladewig	Pelc II	Poldrugo	Tempesta	UKMAS	US 96.1
Hgb	X	X	X	X	X	X	X	X
Hct	X	X	X	X	X	X	X	X
RBC	X	X	X	X			X	X
WBC	X	X	X	X	X	X	X	X
Platelets	X	X	X	X			X	X
MCV	X	X	X	X	X	X	X	X
MCH	X							X
MCHC	X							X
Differential	X							X

(table constructed by reviewer from information in submission)

The number of patients for whom data is available varies by parameter. Hemoglobin, hematocrit, white blood cell counts, and MCV were measured at baseline in over 1000 patients in each of the acamprosate 1998/2000 mg/day group and placebo group, and post-baseline values are available from roughly 900 patients in each group. Normalized values for platelets are available from roughly 800 patients in each group at baseline and post-baseline values for over 600 patients. MCH, MCHC, and white cell differentials are available for 400

patients in the acamprosate 1998/2000 mg/day group and 403 in the placebo group, and post-baseline for 360 acamprosate and 368 placebo patients. (See appendix.)

In the long-term Group I studies, hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets and MCV were collected in studies Barrias, Besson, and PRAMA. Study Lesch collected all parameters except MCV, while Paille collected only MCV. Post-baseline data are available on roughly 325 patients in the acamprosate 1998 mg/day group and nearly 400 in the placebo group.

Taken together, the short-term and long-term group I studies provide post-baseline data on basic hematologic parameters for over 1000 patients, with the exception of platelets, for which data is available for slightly fewer than 700 patients. Coagulation parameters were not assessed.

However, only values normalized to the upper limit of normal were submitted for review for a subset of these studies. Actual, observed, values were not submitted from BENELUX, Ladewig, Poldrugo, or UKMAS. Only the data from ADISA, Pelc-II, Tempesta, and US 96.1, and PRAMA were submitted as actual values with normal ranges, and only for these studies did Lipha identify “clinically significant abnormalities” for hematologic parameters. For Paille, Lipha identified “clinically significant abnormalities” for MCV only.

7.1.6.3 Clinical Chemistry

The 13 Group I Studies collected chemistry laboratory blood tests routinely. The specific panel collected varied by study.

All 8 short-term Group I studies collected total bilirubin, AST, ALT, GGT, alkaline phosphatase, creatinine, BUN, uric acid, sodium, potassium, chloride, calcium, phosphorus, glucose. Values for glucose and phosphorus were not available from all studies except the UKMAS study. In addition, study US 96.1 collected LDH, total protein, albumin and bicarbonate.

For the fourteen parameters collected by all studies, the safety population includes 2564 patients, 135 patients assigned to acamprosate 1332 mg/day, 1128 patients to acamprosate 1998/2000 mg/day, 83 patients to acamprosate 3000 mg/day and 1218 patients to placebo. The pooled acamprosate group consists of all patients from the 3 acamprosate dosage groups (1346 patients). However, because of variability in collection of clinical chemistry samples, the N for each parameter was calculated and displayed separately by Lipha. There is no parameter for which data are available for the predicted number of patients (e.g. 1128 patients in acamprosate 1998/2000 mg/day group). However, overall, approximately 800-850 patients were included in change from baseline calculations for chemistry parameters, with the exception of those collected only in the US 96.1 study.

In the 5 long-term Group I studies, clinical laboratory collection was more variable. As shown in the table below, the most complete data is from studies Barrias, Besson, Lesch, and PRAMA.

Clinical Chemistry Assessments in Group I Studies

	Barrias	Besson	Lesch	Paille	PRAMA
T Bili	X	X	X		X
AST	X	X	X	X	X
ALT	X	X	X	X	X
GGT	X	X	X	X	X
Alk Phos	X	X	X		X
Creatinine	X	X	X		X
BUN	X	X	X		
Uric Acid	X	X	X		X
Na	X	X	X		X
K	X	X	X		X
Cl	X	X	X		
Ca	X	X	X		X
Phos	X	X	X		
Total Protein					X

The overall safety population for the long-term studies includes 621 patients in the acamprosate 1998/2000 mg/day group, 926 in the acamprosate pooled group, and 744 in the placebo group. However, because of variability in collection of clinical chemistry samples, the N for each parameter was calculated and displayed separately by Lipha. There is no parameter for which data are available for the predicted number of patients. However, overall, approximately 300 patients were included in change from baseline calculations for each parameter, other than AST/ALT/GGT, for which just under 600 patients were included. Taken together with the short-term studies, this provides over 1000 patients included in the analysis for most clinical laboratory parameters. Information is more scant on total protein, albumin, LDH, and bicarbonate.

However, only values normalized to the upper limit of normal were submitted for review for a subset of these studies. Actual, observed, values were not submitted from BENELUX, Ladewig, Poldrugo, or UKMAS.

7.1.6.4 Analyses and Explorations of Data

7.1.6.4.1 Hematology

Because multiple clinical laboratories were used in the Group I studies, the data were reported and analyzed as normalized values, presented as the percentage of actual values relative to the ULN at the respective laboratory. A normalized value >100 indicates a value greater than the ULN. A normalized value ≤100 indicates a value below or equal to the ULN. Unfortunately, no normalization to the *lower* limit of normal appears to have been performed.

7.1.6.4.1.1 Measures of Central Tendency

Examination of the mean normalized values at baseline and changes from baseline to endpoint in the Group I short-term studies reveals that there were minimal differences between the acamprosate-treated and the placebo-treated groups.

7.1.6.4.1.2. Outliers and Shifts from Normal to Abnormal

Hematologic abnormalities were common. Among the most common abnormalities occurring at any post-Baseline visit were red blood cell counts below the lower limits of normal (ranging in incidence from 17% in the acamprosate 3000 mg/day group to 35% in the acamprosate 1332 mg/day group) and MCV values >105 fl (ranging in incidence from 5% in the acamprosate 1332 mg/day group to 11% in the placebo group).

Because analysis of outliers was performed by Lipha primarily using data normalized to the *upper* limit of normal, the dataset of actual lab values was used in a reviewer's analysis of abnormally low values for hematologic parameters. The dataset SS_LABAN was used to determine how many subjects had at least one non-baseline value for platelets, WBC, and RBC. This dataset contains data from studies ADISA, PRAMA, Paille, Pelc-II, Tempesta, and US 96.1 only. The number of patients with abnormally low values was then determined, and compared across treatment groups. Because of alcohol's multiple hematologic toxicities, abnormalities at baseline were common. The analysis focuses on abnormalities emerging in patients with values above the lower limit of normal at baseline, or for whom no baseline value is in the dataset.

In dataset SS_LABAN, 1193 patients had at least one non-baseline measurement of platelets (74 acamprosate 1332 mg/day; 517 acamprosate 1998 mg/2000 mg/day; 71 acamprosate 3000 mg/day; 531 placebo). There were 46 patients with at least one platelet count below $100 \times 10^3/\mu\text{l}$. Of these, 29 had an abnormally low platelet value at baseline. Of the 17 subjects with normal (or undocumented) levels at baseline, two were treated with acamprosate 1332 mg/day, 7 with acamprosate 1998 mg/2000 mg/day, one with acamprosate 3000 mg/day, and 7 with placebo, representing 3%, 1%, 1%, and 1%, respectively, of the patients with post-baseline platelet measurements in each group. Three of these patients, treated with placebo, had an adverse event of "thrombocytopenia" reported and one, treated with acamprosate 2000 mg/day, had an event "platelet count decreased." No bleeding-related adverse events were reported. Thus, there did not appear to be an effect of acamprosate on platelets based on this analysis.

Non-baseline WBC measurements were available for 1499 patients, including 75 treated with acamprosate 1332 mg/day, 669 with acamprosate 1998 mg/2000 mg/day, 72 with acamprosate 3000 mg/day, and 683 with placebo. One-hundred and eleven patients had at least one WBC count below the lower limit of normal. Of these, 88 had a normal (or undocumented) WBC count at baseline. The 88 patients included 4 treated with acamprosate 1332 mg/day, 32 with acamprosate 1998 mg/2000 mg/day, 5 with acamprosate 3000 mg/day, and 47 with placebo, representing 5%, 5%, 7%, and 7% of the patients for whom post-baseline WBC values were available. Thus, there did not appear to be an effect of acamprosate on WBC based on this analysis.

Hematocrit abnormalities were common. Normalized hematocrit values were available for 3596 patients. Because most of the listings in the tabulation of actual values gave a range of normal values for which the lower limit was 74% of the upper limit, this cutoff was chosen as the method to identify values below the lower limit of normal. Overall 98/242 (41%) in the 1332 mg/day group, 291/1542 (19%) in the 1998 mg/2000 mg/day group, 16/83 (19%) in the 3000 mg/day group, and 328/1729 (19%) in the placebo group had hematocrit values less than

74% of the ULN at some point during treatment.

Actual values for non-baseline hematocrit measurements are available for 1496 patients (75 acamprosate 1332 mg/day; 666 acamprosate 1998 mg/2000 mg/day; 72 acamprosate 3000 mg/day, 683 placebo). Two-hundred and fifty-seven patients had at least one hematocrit below the lower level of normal. Of these, 140 subjects had a normal (or undocumented) hematocrit at baseline. The 140 patients included 7 acamprosate treated with 1332 mg/day; 61 treated with acamprosate 1998 mg/2000 mg/day; 9 treated with acamprosate 3000 mg/day, and 63 treated with placebo, representing 9%, 9%, 13%, and 9% of the patients for whom post-baseline values were available.

Adverse events referable to the hematologic and lymphatic (HAL) body system were reported in 122 patients in the Group I integrated database (1 acamprosate 1332 mg/day; 50 acamprosate 1998 mg/2000 mg/day; 8 acamprosate 3000 mg/day, 63 placebo). The most common terms were anemia, hypochromic anemia, and macrocytic anemia, representing 46% of the events involving the HAL body system. These reports were evenly distributed across treatment groups. Other terms including leukocytosis, leukopenia, lymphocytosis, monocytosis, polycythemia, and thrombocytopenia did not occur at rates suggesting drug relatedness. However, eosinophilia was reported in six subjects, all of whom were acamprosate-treated. Only two studies, US 96.1 and BENELUX, measured WBC differentials, and all of these subjects were in the US 96.1 study. Five subjects were treated with acamprosate 2000 mg/day and one was treated with 3000 mg/day (2.2% and 1.3%, respectively, of the patients for whom post-baseline eosinophil counts were available, vs 0 in the placebo group). Eosinophilia may be indicative of an allergic process; however, the US 96.1 study enrolled patients who may have been abusing other substances, and eosinophilia is very common among intravenous drug users.

Three patients reported hematologic abnormalities in association with premature treatment discontinuation. In one case, hematologic abnormalities were present at baseline.

- One patient, on acamprosate 2000 g/day (US 96.1 pt 21020) was discontinued from study treatment due to anemia (Hgb 10.9 g/dl at discontinuation) occurring in the context of gastritis and melena.
- One patient, on acamprosate 1998 mg/day (Lesch, Patient 194), missed the second scheduled visit, at study day 90, and subsequently the site learned that he had been hospitalized on approximately study day 40, for an exanthem and a hematologic disorder (coded to "blood dyscrasia" [Hemic and Lymphatic System]). No further detail is available. The patient had an elevated WBC count at Baseline (11,000) but a normal value on day 30. Patient was apparently discontinued from the study.
- Another patient, on placebo (Lesch, Patient 281), was discontinued from study participation because of the adverse event of "thrombocytopenia" (Hemic and Lymphatic Disorders) detected on baseline labs. Evidently, labs were reviewed after entry and the patient appears to have been discontinued after two weeks of treatment when the baseline lab abnormality was discovered. The thrombocytopenia was attributed to a concomitant medication (Tegretol) that the patient was taking.

7.1.6.4.2 Clinical Chemistry

Because multiple clinical laboratories were used in the Group I studies, the data were reported and analyzed as normalized values, presented as the percentage of actual values relative to the ULN at the respective laboratory. A normalized value >100 indicates a value greater than the ULN. A normalized value ≤100 indicates a value below or equal to the ULN.

7.1.6.4.2.1 Measures of Central Tendency

In the short-term Group I studies, no major differences from placebo were noted in the mean change from baseline to endpoint for the various clinical chemistry parameters, with the exception of GGT, AST, and ALT, which were all elevated at baseline and showed a greater degree of normalization (mean decrease from baseline) in acamprosate-treated patients compared to placebo-treated patients. Both the elevations at baseline and improvements with treatment are expected in a population of treated alcoholic patients.

In the long-term Group I studies, differences between treatment and placebo included: a mean decrease in total bilirubin vs. a slight increase in placebo; a mean decrease in AST, ALT, GGT to a greater degree than seen in placebo group, and lower mean increase in uric acid (0.8 normalized units vs 3.3) in treatment vs. placebo.

7.1.6.4.2.2 Outliers and Shifts from Normal to Abnormal

Shift tables were constructed by Lipha reflecting changes from baseline to endpoint. However, a limitation of the shift tables is that shifts from abnormality to greater or lesser degrees of abnormality are not reflected in the table. Because of the high rate of baseline abnormality in certain parameters, this approach to shift analysis may not be sensitive to drug effects. Shift tables were constructed for only selected parameters: total bilirubin, AST, ALT, GGT, alkaline phosphatase, creatinine, blood urea nitrogen, calcium and inorganic phosphorus. No differences between acamprosate and placebo were evident in the shift tables, either with respect to shifts from normal to abnormal or with respect to shifts from abnormal to normal.

To detect the development of abnormalities in patients with abnormalities at baseline, as well as to identify shifts of potential significance within the normal range, Lipha's submitted dataset of normalized values was used to identify patients for whom an increase of 30% over the baseline value for any analyte was reported. The number of patients for whom change-from-baseline values were available for any analyte was tabulated, and compared to the number in whom any change in baseline exceeded +30%. Changes of this magnitude were common for several analytes, but there was no difference across treatment groups in the percentage of patients experiencing these changes.

In the Controlled Short-Term studies, there were 4 patients on acamprosate (3 in the acamprosate 1998/2000 mg/day group and 1 in the 3000 mg/day group) who discontinued study participation prematurely because of a laboratory abnormality. No placebo patients discontinued for laboratory abnormalities. In the Controlled Long-Term studies, there were 2 patients on acamprosate (1332 mg/day) and 2 patients on placebo who discontinued study participation prematurely because of a serious adverse event that included a laboratory

abnormality or an equivalent clinical diagnosis. Among the 6 acamprosate patients, the clinical laboratory events leading to discontinuation included:

One patient was withdrawn during the first study week. Terms "gastroenteritis" and "hypokalemia" were listed as adverse events associated with discontinuation, but both baseline and termination potassium values were in normal range. Another patient was discontinued for various complaints including abdominal cramps, chest pain, insomnia, anorexia and mood swings. At the time of discontinuation, he was also found to have a mild increase in SGPT (ALT) and this was given as one of the reasons for his study discontinuation.

One patient was withdrawn for persistent hypokalemia.

In the long-term studies, one patient (Paille, Patient 322), on **acamprosate 1332 mg/day**, with known insulin-dependent diabetes mellitus, was hospitalized prior to Day 60 because of severe "hypoglycemia" (Metabolic and Nutritional Disorders). He was treated and continued in the study until Day 180, at which time he was terminated because of alcohol relapse. Another patient (Paille, Patient 448), on **acamprosate 1332 mg/day**, was withdrawn because of the serious adverse events of severe alcohol relapse, "atrial flutter", "hyperglycemia" and "lab test abnormal" Although the narrative indicated that these values included elevated serum creatinine and mildly abnormal liver function tests, requiring further treatment and medical evaluation, the values are not included in the submitted data. Further inquiry and review of available information by Lipha revealed that the narrative was in error, and that elevated creatine kinase, not creatinine, was documented. This patient had a screening serum creatinine of 77 micromoles/liter (normal range for adult male, 53 to 106 micromoles/liter). In the Paille study, no further monitoring of serum creatinine was done on a routine basis. This patient was hospitalized with atrial flutter, at which time he was found to have marked hyperglycemia (15.2 mmol/liter with normal range of 4 to 5.5 mmol/l), a SGPT of 52 (normal < 50), a SGOT of 74 (normal <40), a serum creatine kinase (CK) of 215 (Normal range 15 to 130) and a gamma glutamyl transferase (GGT) of 554 (normal <40). His hemogram was essentially normal except for a red blood cell MCV of 96.2 (ULN 92.0) and a slightly reduced platelet count (125,000/mm³). These values occurred in the context of an alcohol relapse and the atrial flutter.

7.1.6.5 Vital Signs

7.1.6.5.1 Extent of Vital Signs Testing in the Development Program

Although there was some measurement of vital signs (systolic and diastolic blood pressure and pulse) and/or body weight in 11 of the 13 Group I studies (excluding the Short-Term studies **Tempesta** and **Ladewig**), only **Pelc II** and **US 96.1** among the Short-Term studies and **PRAMA** and **Paille** among the Long-Term studies had regular measurements of all vital signs at each study visit. Data from these studies was tabulated by Lipha (short-term separate from long-term studies). Vital sign data from the other Group I studies were summarized, as available, based on results in the respective final study reports. Therefore, the safety population for vital sign and weight assessment includes 789 in the short-term studies (3-6 months), consisting of 63 patients on acamprosate 1332 mg/day, 321 patients on acamprosate 1998/2000 mg/day, and 322 patients on placebo. In the long-term studies, the safety population includes 810 alcohol-dependent patients, consisting of 212 patients on

acamprosate 1332 mg/day, 285 patients on acamprosate 1998 mg/day, and 313 patients on placebo.

Vital signs were also assessed in 21 of the 33 completed Group II Clinical Pharmacology studies, involving 335 patients.

Of the Group III studies, only one provided by-patient listings permitting assessment of the effect of acamprosate on vital signs. This study, Lhuintre, included 279 patients treated with acamprosate 1332 mg/day and 290 treated with placebo.

Among the Group IV studies, data on group mean values for vital signs are available for a subset of the studies.

7.1.6.5.2 Analyses of Vital Signs

No differences between treatment groups were noted in analyses of group means. Analysis of occurrence of abnormal vital signs were presented by Lipha using the following definitions:

Definitions of “Clinically Significant” Abnormalities in Vital Signs and Body Weight

“Clinically Significant” Abnormalities of Vital Signs	
Systolic blood pressure:	≥180 mm Hg and ≥20 mm Hg above Baseline value ≤90 mm Hg and ≥20 mm Hg below Baseline value
Diastolic blood pressure:	≥105 mm Hg and ≥15 mm Hg above Baseline value ≤50 mm Hg and ≥15 mm Hg below Baseline value
Pulse rate:	≥120 bpm and ≥15 bpm above Baseline value ≤50 bpm and ≥15 mm bpm below Baseline value
Body weight:	Increase ≥7% of Baseline Decrease ≥7% of Baseline

The percentage of patients with clinically significant changes in systolic and diastolic blood pressure, and pulse rate (increase or decrease) was similar between the acamprosate 1998/2000 mg/day, pooled acamprosate and placebo treatment groups. The only acamprosate-related effect of clinical significance was observed in the Jaillon study, a Group II clinical pharmacology study. This was a 4-period crossover study of single i.v. doses of placebo and acamprosate at 10, 20 and 30 mg/kg, given by infusion over 10 minutes to 12 healthy male volunteers. Significant decreases in heart rate were observed at i.v. acamprosate doses of 20 and 30 mg/kg. With i.v. acamprosate 20 mg/kg, the mean heart rate was significantly decreased at 15 and 30 minutes post-infusion, relative to placebo (54.2 ± 6.4 vs 61.2 ± 5.6 at 15 minutes and 53.3 ± 7.6 vs 60.7 ± 6.0 at 30 minutes). With i.v. acamprosate 30 mg/kg, the mean heart rate was significantly decreased between time points of 5 minutes to 1 hour, with the maximum effect at 20 minutes post-infusion, relative to placebo (49.8 ± 6.7 vs 58.8 ± 6.3 at 20 minutes). There were no effects on blood pressure or evidence of orthostasis in this study and no effect on ECG intervals or cardiac rhythm. Maximum acamprosate blood levels (occurring at 15 minutes) were 41.8, 88.1 and 139.2

mg/L at the 10 mg/kg, 20 mg/kg and 30 mg/kg dose levels, respectively. These compare to the usual mean acamprosate blood levels at the therapeutic oral dose of 1998 mg/day of 353 µg/L.

The only other acamprosate-related effect on vital signs was an apparent effect on body weight in some studies. Notably, clinically significant changes in body weight were reported in a substantial proportion of patients in the long-term, but not the short-term, studies. The percentage of patients with clinically significant increases in body weight (>7%) in the short-term studies was 8% in the pooled acamprosate group and 6% in the placebo group. Clinically significant decreases in weight (>7%) were reported by 5% of the pooled acamprosate group and 7% of the placebo group. However, in the long-term studies, clinically significant increases in weight were reported in 27% of the pooled acamprosate group vs. 19% in the placebo group. Weight decrease was reported by 26% of the acamprosate 1332 mg/day group, 15% of the acamprosate group 1998 mg/day group, and 13% of the placebo group. Weight increase may be partially explained by successful treatment of alcoholism and the improvements in nutritional status that may ensue; however increases in body weight were also seen in some pre-clinical studies, and may represent an effect of the drug. The mechanism is unclear, as effects on appetite were mixed and inconsistent. Increased appetite was reported as an AE by approximately 1% of each treatment group (3/397 of patients in the 1332 mg/day group, 22/1539 in the 1998mg/2000mg/day group, and 13/1706 in the placebo group.) Conversely, anorexia was reported as an AE by 20 (5%) patients in the 1332 mg/day group, 35 (2%) in the 1998mg/2000mg/day group, 2 (2%) in the 3000 mg/day group and 44 (3%) in the placebo group.

7.1.7 ECGs

ECG testing in the development program for acamprosate was limited. During the first cycle review, the paucity of clinical ECG data was noted, along with the lack of information about the effects of acamprosate on cardiac conduction from animal and *in vitro* studies. New preclinical information on the cardiac effects of acamprosate has been submitted for this review cycle, and demonstrates that acamprosate did not show adverse effects in the hERG channel assay or in the dog Purkinje fiber assay. An *in vivo* study in beagle dogs demonstrated no cardiac conduction effect of acamprosate at maximum plasma levels approximately 200- to 700-fold higher than the C_{max} associated with the usual therapeutic human dose.

7.1.7.1 Extent of ECG Testing in the Development Program

Only two of the controlled Group I studies, U.S. 96.1 and UKMAS measured ECG's at baseline and on-treatment. The information reported included the prevalence of "abnormal" readings and the number of shifts from normal to abnormal. Only ECG's from the US study appear to have been available for re-evaluation.

In addition, ECG's were performed at baseline and on-treatment for a subset of the Group II Clinical Pharmacology studies. For some, only summary results were available from study reports, and no significant drug-induced changes were noted. The Division requested that blinded manual readings be obtained and retrospectively analyzed for four dose-escalating pharmacokinetic studies, Dewland I, Dewland II, Theodor II, and Jaillon. ECG's were not

available for Jaillon, but Lipha obtained ECG's from the other three studies, as well as from an additional Group II study, Theodor I.

Therefore, the extent of ECG testing for which tracings could be manually read by a centralized, blind reader was limited to four Phase I and one Phase III study.

In the Phase I studies, the number of subjects for which ECG's were available were:

Single dose											
	Placebo	333 mg		666 mg		1332 mg		1998 mg	2664 mg		
	6*	6		12		12		6	12		
Multiple dose											
	Placebo		600 mg		1000 mg	1332 mg	1600 mg	1998 mg	2664 mg	3996 mg	5328 mg
	18**		12		12	6	14	36	6	6	6

In the US 96.1 study, 102 ECG's from patients treated with acamprosate were re-read by a central lab, including 68 patients treated with acamprosate 2000 mg/day, 34 treated with acamprosate 3000 mg/day. Additionally, ECG's were reevaluated from 88 patients treated with placebo. Therefore, ECGs from 156 subjects treated with acamprosate at the recommended daily dose or higher, measured at baseline and steady state after multiple dosing, are available to assess the effect of acamprosate on cardiac conduction.

7.1.7.2 Overall Drug-Control Comparisons

7.1.7.3 ECGs in Clinical Pharmacology Program

The tables below show the effect of acamprosate on ECG in single- and multiple-dose Phase I studies for which ECG's were available for reevaluation. The only notable effect observed in the single-dose studies was a higher number of heart rate outliers (all bradycardia) in the highest dose group; this is consistent with a bradycardic effect of acamprosate seen in the Jaillon study, a Phase I study involving intravenous administration of very high doses of acamprosate. In the multiple-dose studies, both modest (30-60 msec) and more significant (>60 msec) degrees of QT prolongation were noted in the acamprosate groups than in the placebo group using the Bazett correction; however the effect was not clearly dose-dependent. No increases of >60 msec were seen when the Fridericia correction was applied.

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Acamprosate Single Dose Effect on Mean Change from Baseline (Δ) and New Outliers for Selected ECG Measurements—Group II Integrated Trial Data (Dewland I and Dewland II)

ECG-Related Parameter	Acamprosate Single Dose Groups					
	Placebo n = 12*	333 mg n = 6	666 mg n = 12	1332 mg n = 12	1998 mg n = 6	2664 mg n = 12
Δ Heart Rate in bpm	-2	-4	-3	-1	-2	-4
Heart Rate Outliers (N,%) all bradycardia events	1 (8%)	0	2 (17%)	0	0	4 (33%)
Δ PR in msec	0	-1	1	1	5	-2
PR Outliers (N,%)	0	0	0	0	0	0
Δ QRS in msec	-3	-1	0	-1	-1	0
QRS Outliers (N,%)	0	0	0	0	0	0
Δ QT in msec	1	3	3	3	4	6
QT new >500 msec	0	0	0	0	0	0
Δ QTcB in msec	-3	-11	-9	-4	-3	-11
QTcB new >500 msec (N,%)	0	0	0	0	0	0
Δ QTcB 30-60 msec (N,%)	3 (25%)	0	0	3 (25%)	0	2 (17%)
Δ QTcB >60msec (N%)	1 (8%)	0	0	0	0	0
Δ QTcF in msec	-1	-7	-5	-2	-1	-6
QTcF new >500 msec	0	0	0	0	0	0
Δ QTcF 30-60 msec (N,%)	1 (8%)	0	0	1 (8%)	0	1 (8%)
Δ QTcF >60 msec	0	0	0	0	0	0
New abnormal U waves (N,%)	0	0	0	0	0	0

Data Source: Submission to NDA of September 5, 2003 (Amendment #033).

Sponsor's In-Text Table 8.8.13.3.1:1.

* 6 unique pts dosed twice with placebo = 12 pt equivalents

Note: Studies included in this table (and the original NDA volume number of the respective study reports) are: Dewland I (Vol. 40) and Dewland II (Vol. 41). These studies are summarized in Volume 62, Section 8.3 of the original NDA.

Note: Bpm=beats per minute; msec=milliseconds; QTcB: Bazett correction; QTcF= Fridericia correction; "new" means not present at baseline, i.e. at any evaluation pre dose, and only seen post baseline.

Acamprosate Multiple Dose Effect on Mean Change from Baseline (Δ) and New Outliers for Selected ECG Measurements—Group II Integrated Trial Data (Dewland I, Theodor I and Theodor II)

ECG-Related Parameter	Acamprosate Multiple Dose Groups in Milligrams Per Day (number of subjects)								
	Placebo n = 24*	600 n = 12	1000 n = 12	1332 n = 6	1600 n = 14	1998/ 2000 n = 36	2664 n = 6	3996 n = 6	5328 n = 6
Δ Heart Rate in bpm	5	7	15	0	12	4	-1	1	1
Heart Rate Outliers (N,%)	0	0	0	0	0	0	0	0	0
Δ PR in msec	-3	-1	-10	6	-6	-2	-2	7	-5
PR Outliers (N,%)	0	0	0	0	0	1 (3%)	0	0	0
Δ QRS in msec	1	0	-1	0	0	1	-1	1	0
QRS Outliers (N,%)	0	0	0	0	0	0	0	0	0
Δ QT in msec	-14	-8	-29	3	-28	-16	7	-5	1
QT new >500 msec (N,%)	0	0	0	0	0	0	0	0	0
Δ QTcB in msec	3	11	13	2	4	-4	4	0	4
QTcB new >500 msec (N,%)	0	0	0	0	0	0	0	0	0
Δ QTcB 30-60 msec (N,%)	5 (21%)	0	3 (25%)	0	1 (7%)	3 (8%)	2 (33%)	1 (17%)	2 (33%)
Δ QTcB >60 msec (N,%)	0	0	0	0	0	0	1 (17%)	0	1 (17%)
Δ QTcF in msec	-3	4	-2	3	-7	-8	5	-1	3
QTcF new >500 msec (N,%)	0	0	0	0	0	0	0	0	0
Δ QTcF 30-60 msec (N,%)	4 (17%)	0	1 (8%)	0	0	0	2 (33%)	0	2 (33%)
Δ QTcF >60 msec (N,%)	0	0	0	0	0	0	0	0	0
New abnormal U waves (N,%)	0	0	0	0	0	0	0	0	0

Data Source: Submission to NDA of September 5, 2003 (Amendment #033).

Sponsor's In-Text Table 8.8.13.3.2:1

* From Dewland I, 6 unique subjects dosed twice with placebo = 12 patient-equivalents + 12 subjects from Theodor II = 24
Note: Bpm=beats per minute; msec=milliseconds; QTcB: Bazett correction; QTcF= Fridericia correction; "new" means not present at baseline, i.e. at any evaluation pre dose, and only seen post baseline.

Note: Studies included in this table (and the original NDA volume number of the respective study reports) are: Dewland I (Vol. 40), Theodor II (Vol. 42) and Theodor I (Vol. 47). These studies are summarized in Volume 62, Section 8.3 of the original NDA.

7.1.7.4 ECGs in Controlled Studies

Of the 13 double-blind, placebo-controlled Group I studies in alcohol-dependent patients presented in the NDA, 2 (UKMAS and US 96.1) had ECGs recorded both at baseline and again at the final visit or on-study.

In UKMAS, a 6-month Phase III study of acamprosate 1998 mg/day (289 patients) vs placebo (292 patients) in alcohol-dependent patients, ECGs were performed at baseline, Visit 7 (after 13 weeks of treatment) and at Visit 10 (last visit during the treatment phase). 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 mg/day: 21 patients, 21%; placebo, 19 patients, 18%).

In US 96.1, a 6-month study of acamprosate 2000 mg/day (258 patients) vs acamprosate 3000 mg/day (83 patients) vs placebo (260 patients) in alcohol-dependent patients, ECGs were to be obtained at baseline and at the end of the Treatment Phase. Based on the original individual study site ECG interpretations, the percentage of patients with abnormal, but acceptable ECGs at baseline was similar among the 3 treatment groups: acamprosate 2000 mg/day, 76 patients (30%); acamprosate 3000 mg/day, 29 patients (35%); and placebo, 83 patients (32%). As part of the re-assessment of possible effects of acamprosate on cardiac electrophysiology, based on requests from the Division, ECGs from participants in US 96.1 who had both an evaluable ECG at screening and while on acamprosate (or within 3 days of acamprosate discontinuation) were sent to a central ECG laboratory for reevaluation. ECG measurements were performed using digitization software with magnification of the ECG and point-to-point determination on the digitizing pad by experienced technicians and a centralized cardiologist who was blinded to study treatment. Of the 601 randomized patients in US 96.1, 190 fulfilled this criterion: 88 of 260 patients in the placebo group, 68 of 258 patients in the acamprosate 2000 mg/day group and 34 of 83 patients in the acamprosate 3000 mg/day group.

No significant differences between drug and placebo were observed with respect to morphology, rate, rhythm, or intervals, as shown in the table below.

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Effect on Mean Change from Baseline (Δ) and New Outliers for Electrocardiographic Measurements According to Treatment Group

Parameter	Treatment Groups and Number of Patients in Sample (n)		
	Placebo (n = 88)	Acamp 2000 (n = 68)	Acamp 3000 (n = 34)
Δ Heart Rate in bpm	-3	-2	-1
Heart Rate Outliers (N,%) all bradycardia events	0	1 (1%)	0
Δ PR in msec	1	6	3
PR Outliers (N,%)	0	0	0
Δ QRS in msec	2	0	-1
QRS Outliers (N,%)	0	0	0
Δ QT in msec	3	5	-2
QT new >500 msec (N,%)	0	0	0
Δ QTcB in msec	-5	0	-4
QTcB new >500 msec (N,%)	0	0	0
Δ QTcB 30-60 msec (N,%)	5 (6%)	2 (3%)	0
Δ QTcB >60 msec (N,%)	0	1(2%)	1 (3%)
Δ QTcF in msec	-2	2	-3
QTcF new >500 msec (N,%)	0	0	0
Δ QTcF 30-60 msec (N,%)	4 (5%)	3 (4%)	1 (3%)
Δ QTcF >60 msec (N,%)	0	0	0

Sponsor's Table from Submission 8/28/03

Bpm=beats per minute; msec=milliseconds; QTcB: Bazett correction; QTcF= Fridericia correction; "new" means not present at baseline, i.e. at any evaluation pre-dose, and only seen post-baseline.

7.1.8 Explorations for Predictive Factors

Because very few drug-related adverse events were observed, explorations for predictive factors such as gender, race, age, and concomitant medications are limited. Furthermore, such explorations are complicated by the low enrollment of women (~20%), the lack of information on race from any study other than US 96.1, and the extremely low enrollment of elderly patients (patients over age 65 were excluded from all but the US 96.1 study, and few over 60 were enrolled in any study). However, Lipha undertook these explorations and found no obvious differences in safety profile across subpopulations. With respect to the safety experience of patients using various concomitant medications, Lipha compared the incidence of adverse events in patients using various categories of medications, and also summarized the findings of formal pre-clinical and clinical drug-drug interaction studies. No

evidence for pharmacokinetic interaction of acamprosate with ethanol, diazepam, imipramine, or disulfiram was observed. Co-administration of naltrexone with acamprosate increased the rate and extent of absorption of acamprosate, as indicated by a 33% increase in acamprosate C_{max} , a 25% increase in the AUC_{0-T} and a shorter T_{max} value. Although these differences were statistically significant, their clinical relevance was uncertain. Naltrexone did not affect the elimination half-life of acamprosate. From clinical observation in the ASATIM study involving coadministration of acamprosate with drugs used in the management of acute alcohol withdrawal, there was also no evidence that acamprosate in combination with either barbiturates, meprobamate or benzodiazepenes increased the incidence of adverse events.

7.1.8.1 Concomitant Medications

Lipha also analyzed data the ten Group I Double-Blind, Placebo-Controlled clinical trials which collected spontaneously reported adverse events and consistently listed concomitant medications (6 Short-Term studies: **ADISA, BENELUX, Pelc II, Poldrugo, UKMAS** and **US 96.1** and 4 Long-Term studies: **Barrias, Besson, Paille** and **PRAMA**). These studies collectively involved 3395 patients (1855 in the pooled acamprosate group and 1540 in the placebo group). The incidence of spontaneously reported treatment-emergent adverse events was summarized as a function of various concomitant medications, commonly used in alcohol dependent patients (anti-depressants, anxiolytics, hypnotics and sedatives, histamine H_2 -receptor antagonists and analgesics).

7.1.8.1.1 Antidepressants

Overall, there were 291 patients (9% of 3395) who used antidepressants at some time during the study (174 in the 1855-patient pooled acamprosate group [9%] and 117 in the 1540-patient placebo group [8%]). Patients who did not use antidepressants, collectively, had fewer adverse events than did those who used antidepressants. In patients who did not use antidepressants, there were more adverse events in the pooled acamprosate group (63%) compared to the placebo group (58%). In the group using antidepressants, there were more patients with adverse events in the placebo group (84%), compared to the pooled acamprosate group (78%). Patients taking antidepressants in the pooled acamprosate group had a higher incidence of Metabolic and Nutritional Disorders (13%) compared to the placebo group (5%) and to the the major treatment groups of those not taking antidepressants (6%). This seemed to be accounted for by a higher incidence of events of “weight gain” (5%) and “weight loss” (6%) in those who were taking antidepressants and were in the pooled acamprosate group compared to the placebo group, where the respective events had an incidence of 2% and <1%. In the pooled acamprosate group of patients not taking antidepressants, the incidence of both “weight gain” and “weight loss” was <1%. Both “depression” and “suicide” were more commonly reported among patients treated with antidepressants, as would be predicted. However, in both the group using antidepressants and the group not using antidepressants, the suicide rate was twice as high in the acamprosate group as in the placebo group (6% vs 3% in patients using antidepressants; 0.7% vs 0.35% in patients not using antidepressants).

7.1.8.1.2 Anxiolytics

Overall, there were 739 patients (22% of 3395) who used anxiolytics at some time during the study (430 in the 1855-patient pooled acamprosate group [23%] and 309 in the 1540-patient

placebo group [20%]). Patients who did not use anxiolytics, collectively, had fewer adverse events than did those who used anxiolytics. In patients who did not use anxiolytics, there were slightly more adverse events in the pooled acamprosate group (61%) compared to the placebo group (58%). In the group using anxiolytics, 75% of pooled acamprosate group experienced adverse events, compared to 68% of the placebo group. Overall, although the anxiolytics + acamprosate and the anxiolytics + placebo groups experienced a higher rate of adverse events than the corresponding groups without anxiolytics, the differences between acamprosate and placebo were not notably different in the presence or absence of anxiolytics.

7.1.8.1.3 Sedative/Hypnotics

Overall, there were 261 patients (8% of 3395) who used hypnotics or sedatives at some time during the study (141 in the 1855-patient pooled acamprosate group [8%] and 120 in the 1540-patient placebo group [8%]). No remarkable differences were noted in treatment/control comparisons when the subjects using sedative/hypnotics were compared to those who did not.

7.1.8.1.4 H₂-receptor antagonists

Overall, there were 60 patients (2% of 3395) who used histamine (H₂ blockers) at some time during the study (37 in the 1855-patient pooled acamprosate group [2%] and 23 in the 1540-patient placebo group [1%]). Although the small size of the group renders conclusions questionable, some treatment/placebo differences appeared enhanced in the subgroup using H₂ blockers. The table below illustrates selected AE's where the treatment/placebo differences were apparent only in the subgroup using H₂ blockers, or, in the case of diarrhea, where the odds ratios were quite different in the H₂ blocker subgroup than in the population not using H₂ blockers.

Body System/Preferred Term	Statistic	ACAMP 1998/2000 mg/day N=24	ACAMP Pooled N=37	Placebo N=23	ACAMP 1998/2000 mg/day N=1351	ACAMP Pooled N=1818	Placebo N=1517
Number of patients with an AE	n (%)	24 (100%)	34 (92%)	17 (74%)	847 (63%)	1158 (64%)	901 (59%)
Abdominal pain	n (%)	5 (21%)	8 (22%)	2 (9%)	79 (6%)	104 (6%)	92 (6%)
Diarrhea	n (%)	13 (54%)	16 (43%)	3 (13%)	243 (18%)	312 (17%)	162 (11%)
Dyspepsia	n (%)	5 (21%)	7 (19%)	2 (9%)	32 (2%)	38 (2%)	29 (2%)
Flatulence	n (%)	6 (25%)	7 (19%)	1 (4%)	49 (4%)	56 (3%)	27 (2%)
Vomiting	n (%)	2 (8%)	4 (11%)	1 (4%)	49 (4%)	57 (3%)	47 (3%)
Depression	n (%)	3 (13%)	6 (16%)	1 (4%)	60 (4%)	96 (5%)	86 (6%)
Anxiety	n (%)	2 (8%)	3 (8%)	0	36 (3%)	54 (3%)	37 (2%)
Suicidal ideation	n (%)	1 (4%)	3 (8%)	0	8 (<1%)	107 (<1%)	2 (<1%)

The higher rate of digestive events in the patients using H₂ blockers, and the enhanced treatment/placebo differences, may be explained in two ways. Either these patients were on H₂ blockers at study entry, suggesting a pre-existing gastric condition that may have made them more vulnerable to the digestive effects of acamprosate, or H₂ blockers were prescribed during the study, in part in response to drug-induced digestive symptoms. The higher prevalence of psychiatric symptoms is more difficult to explain, but the differences may be partially due to small sample size.

7.1.8.1.5 Analgesics

Overall, there were 518 patients (15% of 3395) who used analgesics at some time during the

study (279 in the 1855-patient pooled acamprosate group [15%] and 239 in the 1540-patient placebo group [16%]). Patients taking analgesics during the Treatment Phase had a much higher overall incidence of adverse events (91-94%) than did patients who were not taking analgesics (54-59%). However, no major differences in the drug/placebo comparisons were noted between the patients using analgesics and the patients not using analgesics.

7.1.8.1.6 Polysubstance Use

Lipha examined the safety profile of acamprosate in two studies in which testing for illicit drug use was conducted, comparing patients who had at least one positive screen for illicit drugs to patients who did not, and concluded that there was no evidence of an interaction with acamprosate in polysubstance users. However, because of the heterogeneity of the type and amount of illicit drug use, as well as the small number of patients involved, it is difficult to draw conclusions about this data.

7.1.8.1.7 Drug-drug Interactions: Conclusions

In conclusion, based on preclinical studies and clinical studies, there is no evidence of an interaction of acamprosate with ethanol. There is no evidence of a pharmacokinetic interaction of acamprosate and diazepam. Acamprosate does not affect imipramine or desipramine pharmacokinetics or naltrexone pharmacokinetics. Naltrexone increases the rate and extent of acamprosate absorption. There is no effect of disulfiram on acamprosate pharmacokinetics and no clinical evidence of an adverse interaction between disulfiram and acamprosate during co-administration. Acamprosate does not have an adverse clinical interaction when used with meprobamate, barbiturate combinations or oxazepam during acute alcohol withdrawal. Profiles of spontaneously reported adverse events during double-blind, placebo-controlled clinical trials are different in patients using anxiolytics, hypnotics/sedatives or analgesics, but there is no evidence of an interaction of these drug categories with acamprosate. Regarding concomitant use of antidepressants, a treatment/placebo difference was seen in the metabolic and nutritional disorders (primarily weight gain/loss) only in patients using antidepressants. Too few patients were treated with H2 antagonists to conclusively comment on whether or not there might be an interaction with acamprosate; however, some suggestion of a greater treatment/placebo difference for digestive and psychiatric complaints in the presence of H2 antagonists was noted.

7.1.8.2 Drug-Disease Interactions

Lipha explored the adverse event profile for patients with hepatic impairment at baseline and found no differences in the drug/placebo comparisons in this group compared to patients without hepatic impairment at baseline. No explorations of the effect of renal impairment were undertaken as patients with renal impairment were not eligible for inclusion. This represents an area for further evaluation post-marketing.

7.1.9 *Withdrawal Phenomena/Abuse Potential*

The abuse potential of acamprosate was reviewed by Dr. Katherine Bonson of the Controlled Substances Staff (HFD-009), who noted that:

- Acamprosate does not induce self-administration, sedation, hypnosis, or analgesia in animals. However, it does reduce the hyperactivity induced by known drugs of abuse, suggesting that the drug may modulate the dopamine system. Acamprosate does not

affect 5-hydroxytryptamine-induced head twitches, demonstrating it does not act at 5-HT₂ receptors.

- Acamprosate does not generalize to the following Schedule II drugs in animal drug discrimination tests: d-amphetamine, phencyclidine (PCP), or pentobarbital.
- Available epidemiological data from the 39 countries in which acamprosate is currently marketed do not suggest that acamprosate has abuse liability.
- In clinical trials, acamprosate was not associated with symptoms of physical dependence or overdose.
- Subjective information collected from healthy volunteers during pharmacokinetic and dose-tolerance studies using Visual Analog Scales (VAS) related to abuse liability did not produce any data indicative of abuse potential of acamprosate.
- Pharmacokinetic studies show that acamprosate has a slow rise to peak plasma concentrations (4.5 hr) and a long terminal half-life (5.7 hr). This pharmacokinetic profile is not usually associated with high abuse potential.

The Controlled Substances Staff concluded that the available epidemiological, clinical and preclinical data did not suggest abuse liability for acamprosate.

7.1.10 Human Reproduction and Pregnancy Data

Four pregnancies occurred in the Group I studies; three patients were treated with acamprosate (Paille 469; UKMAS 98, UKMAS 688) and one with placebo (Poldrugo 42). The patients discontinued study drug upon diagnosis of pregnancy. One patient terminated the pregnancy and continued in the study (off drug); one patient indicated the intention to do so. No followup information was provided on either of the pregnancies not known to be terminated. Five pregnancies occurred in the Group IV studies. One patient (NEAT Belgium 18/19) experienced vaginal bleeding which was apparently due to spontaneous abortion at 10 weeks of previously undiagnosed pregnancy. One patient (INTEGRAL 88/6) is identified as having been discontinued from the study due to pregnancy; no further information was provided. Another patient (INTEGRAL 77/1) was identified as being pregnant at week 20; no other information was provided. One patient (A.R.E.S. 341) was noted to be pregnant at her three-month visit (first on-treatment visit). Acamprosate was discontinued but meprobamate was continued. The patient delivered a 2.42 kg infant, with normal Apgars, approximately one month prematurely. Based on the date that medication was discontinued and the date of delivery, prenatal exposure was brief. The last reported pregnancy involved a patient who discontinued study medication on September 13, 1999, and was noted on a subsequent visit (October 30, 1999) to be pregnant. Delivery is reported as having occurred on February 16th, 2000; therefore prenatal exposure during the first trimester is assumed. The patient also continued to drink during pregnancy. The patient was delivered by Caesarean section "because the in utero fetal development seemed slow," but the infant is described as normal.

In post-marketing surveillance, there have been 19 reports of prenatal exposure. Eight pregnancies had normal outcomes; in three cases, the pregnancies were terminated (one after diagnosis of fetal malformation). In seven cases the outcomes are unknown. There have been two reports of congenital anomalies. These include a report of "fetal disorder" death in the newborn son of a patient who was intermittently using venlafaxine, chlordiazepoxide, and acamprosate during pregnancy; the infant was born with trisomy 18. Another case reports

elective pregnancy termination at week 19 due to pre-natal diagnosis of anomalies consistent with fetal alcohol syndrome.

Spontaneously Reported Serious and Non-Serious Events Related to Pregnancy from Post-Marketing Pharmacovigilance -- January 31, 1995 through January 30, 2004

Case Ref. Number/ Country	ACAMP ¹	Age	COSTART Preferred Term	Comments
Outcome Known				
1200319/ Switzerland	1998	37	Unintended pregnancy	Acamprosate taken during first 5 weeks of pregnancy. Normal male infant delivered at 39 4/7 weeks.
1200320/ France	1998	30	Unintended pregnancy	Acamprosate taken during first 11 days of pregnancy. Normal infant, without any pathology.
1200331/ France	ND	35	Unintended pregnancy	Acamprosate taken during first 3-4 weeks of pregnancy. Normal birth and normal infant.
1200352/ France	ND	ND	Unintended pregnancy	Known fertility problems, but became pregnant while on acamprosate and meprobamate. Premature delivery of a normal infant.
1200368/ France	1998	41	Unintended pregnancy	Known fertility problems. On acamprosate and drinking during first 5 months of pregnancy. Normal pregnancy outcome.
1200381/ France	1998	38	Unintended pregnancy	Taking acamprosate during pregnancy. Normal newborn at 40 weeks gestation.
1500994/ UK	1998	29	Eclampsia Unintended pregnancy	Taking acamprosate during pregnancy. Healthy male infant delivered after eclampsia during pregnancy. Also taking carbamazepine.
6005069/ France	ND	34	Unintended pregnancy	Normal baby delivered at term in patient treated with acamprosate during pregnancy for unknown period/dose.
1200376/ Spain also listed as case 1200383 for fetal mal-formation	ND	31	Unintended pregnancy	Chronic alcoholic with 2 prior miscarriages, with evidence of fetal abnormalities on echography for the 2 previous pregnancies. Taking acamprosate, venlafaxin (anti-depressant), chlordiazepoxide intermittently during first 6 weeks of pregnancy. Delivered infant who died of trisomy 18 syndrome (Edwards' syndrome).

Case Ref. Number/ Country	ACAMP ¹	Age	COSTART Preferred Term	Comments
5000466/ France also listed as case 5000468 for fetal mal- formation	1332	ND	Unintended pregnancy	Fifth pregnancy in alcoholic female, with prior history of miscarriage. On acamprosate from 2 nd week of pregnancy up to Week 18 of gestation. Underwent elective abortion at Week 19 because of polymalformation and growth retardation consistent with fetal alcohol syndrome. Normal karyotype.
1200310/ France	2664	35	Unintended pregnancy	Acamprosate taken for 2 months, followed by elective abortion. Also on disulfiram.
1200323/ France	1332	35	Unintended pregnancy	Taking acamprosate and also paroxetine and alprazolam for depression. Stopped all medications at 26 days gestation. Echography normal at 7.5 weeks, but had elective abortion.
Outcome Unknown				
1200293/ France	1998	31	Unintended pregnancy	Acamprosate taken during first 3.5 months of pregnancy. Outcome of pregnancy unknown.
1200311/ France	999	26	Unintended pregnancy	Acamprosate taken during first 17 days of pregnancy. All drugs were discontinued. Outcome of pregnancy unknown.
5001608/ France	ND	ND	Unintended pregnancy	Poorly documented case. Taking acamprosate during first 2 months of pregnancy. Outcome unknown.
5001838/ Switzerland	999	27	Unintended pregnancy	Poorly documented case. Alcoholic mother on acamprosate during pregnancy. First ultrasound at W11 normal. Outcome unknown.
5003371/ France	ND	ND	Unintended pregnancy	Acamprosate taken during first 6 weeks of pregnancy. Outcome unknown.
6004683/ UK	ND	25	Unintended pregnancy	Patient found to be 15 weeks pregnant; date of acamprosate treatment initiation unknown. Outcome unknown.
6006492/ Australia	ND	ND	Unintended pregnancy	Report of acamprosate treatment in a patient at 17 weeks pregnancy. Outcome unknown.

Modified from Lipha's In-Text Table 8.8.9.9:2

Preclinical data suggest acamprosate has the potential for teratogenicity. However, alcohol is a known an potent teratogen. Therefore, in the absence of more specific human pregnancy outcome information, clinicians may wish to weigh the benefits of acamprosate in a patient who is experiencing clinical success with the product against the risks of returning to

drinking alcohol during pregnancy. More information about the safety of acamprosate in pregnancy is needed.

7.1.11 Overdose Experience

Since acamprosate has been commercially available (France, 1989), there have been 21 cases of overdose, almost entirely intentional, which have been reported to the sponsor (includes safety update). This does not include reports of intentional overdoses reported to Lipha's Drug Safety Department during clinical trials. The number of 333 mg tablets ingested has ranged from as few as 13 to as many as 168, equivalent, respectively, to a range of 4.33 to 56 g of acamprosate. In most of the cases, other drugs and/or alcohol were taken, in addition to acamprosate.

Acamprosate blood levels have not been measured and/or reported, with the exception of one case in which levels were found to be within the therapeutic range. Because acamprosate is a calcium salt (although only contributing 33 mg calcium per 333 mg tablet), calcium levels were measured in 3 cases where reported acamprosate tablet ingestion was 30 g, 28 g, and 26.6 g, respectively. In all 3 cases, serum calcium levels were normal. In some cases, the effect on the patient was not reported. In 5 cases, the patient was described as asymptomatic. Diarrhea and syncope were each reported in two cases. Somnolence, drowsiness, agitation and confusion were reported in cases involving multiple drug ingestions, including drugs known to cause these symptoms (e.g. benzodiazepines). One reported case involved an overdose of acamprosate and paroxetine. The patient developed pyrexia, seizures, and cardiac arrest. Autopsy suggested that death was due to alcohol withdrawal syndrome. In another case, a patient took 15 acamprosate tablets on a single day and developed acute tubular necrosis 15 days later. Other medications included furosemide, alprazolam, dipotassium chlorazepate. Renal biopsy confirmed acute tubular necrosis. Complete recovery occurred after two dialysis sessions.

Only four cases involving overdose of acamprosate were reported in the clinical trials. No specific adverse events were noted in these cases, involving ingestion of up to 50 tablets of acamprosate.

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7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS

The overall safety exposure is sufficient to characterize the profile of acamprosate. Information on deaths and SAEs has been captured from over 6000 patients treated with acamprosate. Common, non-serious adverse events have been assessed in over 2000 patients, and vital signs in over 1000. Laboratory values and ECG's have been assessed in a smaller number of patients, but supporting information from animal studies and *in vitro* studies provides reassurance. However, it should be noted that the experience in women, elderly patients, racial minorities, and patients with renal impairment is limited.

7.2.1 Extent and Adequacy of Overall Clinical Experience

7.2.1.1 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

As noted above, the ascertainment of various safety parameters was variable within the sponsor's development program. Deaths and SAEs were captured from a large number of studies, both controlled and uncontrolled, while common AE's were captured from a smaller subset of studies, all controlled. Clinical testing was incorporated in only a subset of controlled studies and clinical pharmacology studies. Overall, the safety exposures for the various parameters were:

	Acamprosate	Placebo
Deaths	7481	2406
SAEs	6090	2295
Common AEs	2019	1706
Lab values	200 – 1700+	<200 – 1400+
Vital signs	1160	925
EKGs	248	112

7.2.1.1.1 Primary Source Data (Development Program)

The primary source data for this review consisted of the Group I studies in which spontaneous adverse events were captured. These included seven short-term (generally 6 months) and four long-term (generally one year) studies enrolling 2019 patients treated with acamprosate and 1706 patients treated with placebo.

The table below illustrates the study visit schedules for the Group I studies. As illustrated, the intensity of monitoring was variable, ranging from 7 on-treatment visits within 3 months to as few as 3 on-treatment visits within 6 months, or 5 within a year. The extent to which this casts doubt on the validity of any analysis which relies on reconstruction of drinking data day by day has already been discussed. However, it must also be pointed out in considering the extent of the safety data.

Study name	Duration	Number & timing of On-treatment Visits
Pelc-II	90 days	7: 8, 15, 30, 45, 60, 75, 90
US 96.1	24 weeks	8: 7, 14, 28, 56, 84, 112, 140, 168
UKMAS	24 weeks	7: 14, 21, 35, 60, 90, 120, 150, 175
ADISA	6 months	6: 8, 30, 60, 90, 135, 180
Tempesta	6 months	6: 30, 60, 90, 120, 150, 180
Benelux	6 months	5: 30, 60, 90, 135, 180
Ladewig*	6 months	3: 30, 90, 180
Poldrugo	6 months	3: 30, 90, 180
Paille	360 days	9: 30, 60, 90, 120, 150, 180, 240, 300, 360
PRAMA	48 weeks	6: 28, 56, 84, 168, 252, 336
Lesch*	360 days	5: 30, 90, 180, 270, 360
Barrias	360 days	5: 30, 90, 180, 270, 360
Besson	360 days	5: 30, 90, 180, 270, 360

*Did not capture spontaneous adverse events

Because the US 96.1 study featured the most intense monitoring, and also enrolled a population more representative of the target population for marketing (i.e., no age restrictions, fewer medical restrictions), the adverse event experience in this study is considered the most relevant for characterizing the safety profile. The adverse event experience from other Group I studies was generally consistent with the US 96.1 trial.

7.2.1.1.2 Secondary Source Data

Because of the lack of availability of case report forms and the lack of information on non-serious adverse events, the study groupings II-IV are generally considered secondary source data. However, these provided a significant amount of information on deaths and serious adverse events. Including the safety update, deaths were captured from an additional 5462 acamprosate-treated patients (beyond the 2019 in the Group I data), and from an additional 700 placebo-treated patients. Serious adverse events were captured from a subset of these studies, providing SAE data on an additional 4071 acamprosate-treated patients and 589 placebo-treated patients. The majority of these exposures were from Group IV open-label studies of 6 months' duration.

Other secondary source data included pharmacovigilance reports, which provided limited information on the specific cases.

7.2.1.2 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug to characterize the safety experience, but further information is needed on the adverse event profile in women, the elderly, racial minorities, and patients with renal impairment.

The doses used and durations of exposure resembled the to-be-marketed usage, and were adequate to assess safety for the intended use. Chronic use is anticipated for patients who are

clinically successful on acamprosate treatment. Over 100 patients with a duration of treatment of ≥ 52 weeks were included in the safety database of controlled studies.

7.2.2 Adequacy of Special Animal and/or In vitro Testing

Appropriate animal and *in vitro* testing was included to evaluate the cardiac effects of acamprosate. No other special animal tests were requested.

7.2.3 Adequacy of Routine Clinical Testing

Clinical testing, including laboratory values, vital signs, and EKGs, were included in only a subset of Clinical Pharmacology and Group I controlled studies. Overall, the numbers of patients for which this data is available are shown in the table below. The numbers for laboratory values represents the range across various laboratory parameters.

	Acamprosate	Placebo
Lab values	200 – 1700+	<200 – 1400+
Vital signs	1160	925
EKGs	248	112

The extent of laboratory testing is somewhat lacking; however, the extent of baseline laboratory abnormality in this population renders interpretation of laboratory findings very difficult. Weighing against this is the absence of significant laboratory changes in preclinical studies. The extent of EKG testing was also minimal; however, no signal was noted in appropriate animal and *in vitro* assessments of the effect of acamprosate on cardiac conduction. Therefore, the testing is deemed adequate.

7.3 SAFETY CONCLUSIONS

The mortality rate in acamprosate-treated patients is similar to that in placebo-treated patients, as are the causes of death. The causes of death, and most of the serious adverse events, are related to the underlying disease of alcoholism and its known complications, such as traumatic injury, hepatic disease, alcoholic cardiomyopathy, gastrointestinal hemorrhage, and gastrointestinal carcinoma. The most common, apparently drug-related adverse events were diarrhea, nausea, and flatulence. Dropout due to adverse events occurred in a relatively small number of patients (8% of acamprosate-treated patients, as compared to 6% of placebo-treated patients). Diarrhea was cited as a reason for premature discontinuation by 2% of acamprosate-treated patients (vs <1% of placebo-treated). All other terms were cited as reasons for discontinuation by <1% of the treated patients in either group. More commonly cited terms (albeit by small numbers of patients) in acamprosate-treated than placebo-treated patients included headache, suicide attempt, intentional overdose, diarrhea, nausea, depression, anxiety, and somnolence.

Most serious adverse events were attributable to underlying alcoholism or alcohol-related diseases, or had other potential explanations. Some serious allergic reactions without clear alternative explanation, largely dermatologic, were reported but drug-relatedness is not clear.

The adverse event of greatest concern is a consistently higher rate of events of a suicidal

nature occurring in acamprosate-treated patients in both short-term and long-term controlled clinical trials. In both groupings, the rate of such events in the acamprosate group, although low, was three times the rate in the placebo group. Approximately 2.4% of acamprosate-treated patients in controlled studies of approximately a year reported at least one treatment-emergent event of a suicidal nature, as compared to 0.8% of placebo-treated patients. This is weighed against a 12-24% rate of maintaining complete abstinence throughout the year, documented in two of the efficacy studies which used a treatment duration of 336-360 days. Therefore, although clinicians should be alerted to the possibility that acamprosate may increase the risk of suicide, the potential benefit outweighs this risk.

Acamprosate does not appear to have a consistent effect on blood pressure or pulse. In long-term studies, but not short-term (6 months) studies, acamprosate treatment was associated with a greater likelihood of clinically significant increase in weight. Because some weight gain may be partially explained by the nutritional improvement associated with successful treatment of alcoholism, this may not be a primary effect of acamprosate.

The available data do not demonstrate an effect of acamprosate on any laboratory parameters; however, the laboratory data are limited, raw values were supplied for only a subset of studies, and the high prevalence of laboratory abnormalities in the study population limit interpretation of the results. Notably, the effect of acamprosate on coagulation parameters does not appear to have been evaluated in humans; however, no effect was seen in animals.

Based on animal data, *in vitro* studies, and limited human data, acamprosate does not appear to have an effect on cardiac conduction.

The database is derived primarily from European studies which did not enroll elderly patients or patients with renal impairment. The population was also primarily male. Information about race was not captured in these studies, and the population is assumed to be primarily Caucasian. Therefore, these limitations of the data must be noted, and further evaluation post-marketing is warranted to characterize the safety of the product in elderly patients, patients with renal impairment, women, and racial minorities.

8 OTHER CLINICAL ISSUES

8.1 DOSING REGIMEN AND ADMINISTRATION

The re-audited data from the efficacy studies analyzed for this resubmission does not demonstrate any benefit of the 1998 mg/day dose over the 1332 mg/day dose in either of the two studies in which patients were randomized to either dose. In other studies, dose assignment was by weight and dose/response relationships are accordingly confounded. This differs from the conclusion of the original NDA review, in which the 1998 mg/day dose appeared superior to the 1332 mg/day dose. Currently, the sponsor proposes to recommend the 1998 mg/day dose in labeling. In all three efficacy studies, the drug was given with meals. Food effect studies showed that the C_{max} of single-dose acamprosate was decreased by 45% and the AUC was decreased by 23% in the presence of food. However, the effect of food in the multiple-dose, steady-state context has not been evaluated. Because the tested regimen, three times daily with meals, may enhance compliance by serving as a memory aid,

this is the recommended regimen.

Notably, no clear dose-toxicity relationships were delineated. In many cases, the 1332 mg/day group had paradoxically higher rates of adverse events. In addition, the small 3000 mg/day arm included in only the US study had higher rates of adverse events compared to the 2000 mg/day group in some cases.

Dose modification is recommended for renally-impaired patients. As with other renally-eliminated drugs, dose reduction should also be considered in the elderly.

Studies still underway will evaluate the effect of higher doses of acamprosate.

8.2 DRUG-DRUG INTERACTIONS

No drug-drug interactions requiring dose adjustment were identified.

8.3 SPECIAL POPULATIONS

No special dosing considerations were identified based on race or gender. Dose adjustment in the elderly is recommended due to renal clearance of the drug.

No dose adjustment is required in hepatic impairment, but the dose should be reduced in patients with renal insufficiency. Further evaluation of the appropriate dose adjustment for severe renal impairment is recommended post-marketing.

No information has been provided regarding dosing adjustment in pregnancy or nursing. This information should be developed post-marketing, as use in pregnant women is possible.

8.4 PEDIATRICS

Lipha requested, and received, a waiver of the requirement for pediatric studies in pre-adolescent patients. However, safety and efficacy studies should be conducted in adolescent patients. This requirement was deferred until after approval at the sponsor's request.

8.5 ADVISORY COMMITTEE MEETING

An advisory committee meeting was not convened to review this resubmission. A description of the discussion and findings of the advisory committee meeting which considered the NDA is included in the original NDA review. In summary, the Psychopharmacologic Drugs Advisory Committee considered the efficacy portion of the NDA only on 5/10/2002, specifically addressing whether the negative findings in the US 96.1 study should be weighed more heavily than the positive findings from the older, European studies in which efficacy was demonstrated. The PDAC did not feel that the population differences or differences in clinical setting were of sufficient concern to dismiss the applicability of the European data, but noted that the labeling should clearly communicate in which populations the drug had been shown effective.

9 SUMMATIVE ASSESSMENT

9.1 CONCLUSIONS ON AVAILABLE DATA

This application contains substantial evidence of efficacy of acamprosate, when used as a part of a comprehensive management program that includes psychosocial support, in the maintenance abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.

The efficacy of acamprosate in the promoting abstinence in subjects who have not undergone detoxification and achieved an abstinent state prior to beginning acamprosate was studied in a single trial, but efficacy was not demonstrated. Efficacy has not been shown in alcoholics who also abuse other illicit substances.

The application contains adequate data to characterize the safety profile and to establish that the benefits of acamprosate outweigh the risks in the intended population. While the overall exposure is sufficient to characterize the general safety profile, the application lacks information about the effects of the drug in women, the elderly, renally impaired patients, racial minorities, and adolescent populations. The only common, drug-related events are diarrhea and nausea. Key safety concerns are a higher rate of suicide attempts and suicidal ideation in treated patients compared to placebo-treated patients, as well as possible signal of allergic reactions, primarily dermatologic. The carcinogenicity potential has not been fully evaluated in animals; however, given the serious and life-threatening nature of alcohol dependence, this may be completed after marketing approval. Evaluation of safety and efficacy in subpopulations poorly represented in the existing database is recommended.

9.2 RECOMMENDATION ON REGULATORY ACTION

I recommend approval of this application.

9.3 RECOMMENDATION ON POST-MARKETING ACTIONS

9.3.1 *Risk Management Activity*

No formal risk management program or tools beyond labeling are recommended for this product; however, labeling should emphasize the need for clinical monitoring of patients for emergence of depressive symptoms.

9.3.2 *Required Phase 4 Commitments*

Carcinogenicity studies in mice should be repeated.

9.3.3 *Other Phase 4 Requests*

Because alcoholism occurs in adolescents as well as adults, further study in the adolescent pediatric population is recommended.

Because use in pregnancy is anticipated, further study of the safety of acamprosate in pregnant patients is recommended.

[

]

Further study to determine appropriate dosing in severely renally impaired patients is recommended.

9.4 LABELING REVIEW

9.4.1 *Clinical Studies Section*

The clinical studies section has been re-written to emphasize that the drug has been shown effective only in recently-detoxified, non-polysubstance abusing alcoholics who are abstinent at treatment initiation. [] were deleted as they added little information. References to [] were deleted.

9.4.2 *Indications Section*

The indication has been rewritten as noted (underlined material represents additions to sponsor's proposed language):
Indication rewritten:

"CAMPRAL[®] is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with CAMPRAL[®] should be part of a comprehensive management program that includes psychosocial support.

[]

9.4.3 *Other*

Contraindication in nursing mothers was not deemed supported by the Pregnancy Labeling Team. Less restrictive language is proposed. The pregnancy category was changed from - (proposed by Lipha) to C, based on pharmacology/toxicology review. Pharmacodynamic studies regarding sleep and EEG effects were deleted for reasons described in the review above (including uncertain clinical relevance, inappropriate dose selection).

A warning concerning the need for monitor patients for emergence of depressive symptoms or suicidal ideation is added. This was not proposed by Lipha, whose analysis concluded that there was not a higher rate of events of a suicidal nature in the treated group compared to the placebo group.

10 APPENDIX

10.1 DEFICIENCIES FROM NOT APPROVABLE LETTER OF 6/27/02

1. The data submitted in this application are inadequate to establish the efficacy of acamprosate for the treatment of chronic alcohol dependence. Evidence of problems with data reliability in the European studies precludes relying on these data as the sole evidence to support the proposed indication. Perform at least one additional adequate and well-controlled study using current standards of careful methodology for ascertainment of alcohol drinking data, prospective outcome measures, and statistical analysis plans. The study currently being conducted in the United States may serve to fulfill this requirement.
2. The data submitted in this application are inadequate to establish the safety of acamprosate. Methods used to collect adverse event data in all but five of the clinical studies limited the information collected to a prespecified finite list of adverse events, which could potentially bias the adverse event profile of this drug, failing to capture spontaneous events that were unexpected or not included in the list. Perform at least one additional adequate and well-controlled study to supplement the primary NDA database using current standards of careful methodology for reporting and collecting adverse event data.
3. Errors and inconsistencies in the coding of AEs preclude an accurate and meaningful analysis of the safety database. Re-examine the COSTART coding of all AEs and reconcile discrepancies. Two different sets of abbreviations for body system were used. This complicates the generation of adverse event tables organized by body system. Re-code the adverse events dataset using only one set of abbreviations.
4. There was a failure to adequately account for, and inconsistency in the reporting of deaths in this NDA. Re-examine your entire database and identify and report all cases of deaths in all acamprosate clinical trials. Provide case report forms and narrative summaries for each case. Additional fatalities described in pharmacovigilance studies may be reported separately.
5. There is inconsistency in the reporting of serious adverse events (SAEs) in this NDA. Re-examine your entire database and identify and report all cases of SAEs in all acamprosate clinical trials. Provide case report forms and narrative summaries for each case. Include, but do not limit your search terms to: *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, hepatitis, anaphylaxis, agranulocytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, rhabdomyolysis, tumor, birth defect, congenital anomaly.*
6. Examine the reasons for patient discontinuation in order to evaluate the appropriateness of the coding. The reasons for premature discontinuation have been categorized in such a way that some discontinuations due to adverse events or due to lack of efficacy may have

been obscured in the category "other." Re-code all discontinuations to reflect the reason for withdrawal. Provide case report forms for all discontinuations due to adverse events.

7. Examine the safety database for all deaths, serious adverse events, and treatment-emergent adverse events occurring up to 30 days after last exposure to study treatment. Code and report these adverse events appropriately. The characterization of such events is important because of acamprosate's relatively long half-life, and because its central nervous system (CNS) activity may be assumed to be mediated through actions at receptors that may persist after plasma levels are no longer detectable.
8. In the text of the Integrated Summary of Safety (ISS), there was repeated shifting of cohorts of subjects included in various analyses. For every grouping, provide a separate presentation of the denominators so that rates may be calculated. Present rates overall, by treatment group, and by gender, age, and race across treatment groups. The continually changing denominator requires that for every table the specific studies included in the grouping and the resultant N's for each group must be presented with each analysis.
9. 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 AEs, SAEs, deaths, or dropouts due to AEs were included in the ISS and which were not. Provide a full detailed assessment of all AEs, SAEs, deaths, and dropouts due to AEs in the ISS.
10. Submit all future electronic data in a format that will facilitate review. Assign unique patient identifiers for each patient in the NDA. Include this number in all datasets such that merging of datasets can be done with some degree of accuracy. Include treatment assignment in every table of the dataset to avoid the need to merge to determine treatment assignment. Provide data definition tables with the column names in the same order as the dataset, with a comprehensive explanation of each data element, including explanation of the derivation for derived elements.
11. Verbatim terms related to suicide were not coded correctly and consistently. Re-code all such events so that all suicide attempts are identified and all completed suicides are included both as suicide attempt and death. Perform a separate analysis of any suicide, suicidal ideation, or intentional overdose that may have occurred during treatment, and upon withdrawal of the drug.
12. Provide a thesaurus that lists each preferred term and all verbatim terms subsumed under that term. Prior to submission, this thesaurus should be reviewed by an experienced and medically knowledgeable individual and gross errors should be corrected prior to submission. Correct and refine inconsistencies in coding.
13. Discrepancies exist between various electronic files within the safety data files. Resolve the discrepancies across datasets prior to resubmitting the safety datasets.
14. Since acamprosate is renally cleared, it can accumulate significantly in patients with moderate or severe renal impairment when a dosage regimen of 666 mg three times daily is used. Provide pharmacokinetic data on an appropriately adjusted dosage regimen for

these patients that would result in plasma levels comparable to those seen in patients with normal renal function.

15. Provide comparative pharmacokinetic data in elderly subjects relative to young adults, since renal function is diminished in this subgroup, resulting in the potential for significant accumulation of acamprosate. If warranted, based on the results of these data, propose an appropriately adjusted dosage regimen
16. Provide pharmacokinetic data on the effect of disulfiram on the pharmacokinetics of acamprosate.
17. The preclinical evaluation of acamprosate did not include ion-channel studies (i.e., IKR studies, HERG studies) currently recommended for first-in-class new drugs and new chemical entities. Although review of the limited ECG data available did not indicate an effect on cardiac conduction, this review was based on machine-read ECGs. The Agency's standard recommendation is for blinded manual readings by cardiologists to assess the QT interval. Provide blinded manual readings performed by cardiologists for the specific dose-escalating pharmacokinetic studies that were performed in phase 1 to affirm the initial impression that this drug does not effect the QT interval. These studies include: Dewland I (n=18), Dewland II (n=6), Theodor II (n=62), and Jaillon (n=12).
18. Perform a one-month oral toxicity study, including full histopathology, in dogs using adequate doses to either characterize the toxicity profile or achieve the maximum feasible dose.
19. Repeat the gene mutation assay in Chinese hamster V79 cells and the chromosome aberration assay using adequate dosing and procedures according to current standards.
20. Repeat the carcinogenicity study in mice. Either a standard two-year assay or an appropriate alternative model may be performed. The Agency encourages the submission of a study protocol with supporting data for concurrence of dose selection by our Executive Carcinogenicity Assessment Committee prior to initiation of the carcinogenicity study.
21. Insufficient data have been provided to assess the abuse liability of acamprosate. Provide a discrete, comprehensive abuse liability package for review. This package should contain data from the following:
 - In vitro* receptor binding assays to evaluate the affinity of acamprosate for all major central nervous system neurotransmitter systems.
 - Cell biology assays for dopamine, norepinephrine, and serotonin transporter sites.
 - A drug discrimination behavioral test to determine if monkeys identify acamprosate as similar to a benzodiazapine.

Prior to conducting the study, submit the protocol to your IND for

acamprosate for review. In the protocol, identify whether lorazepam or chlordiazepoxide will be used as comparator drugs, the dose of the benzodiazepine to be used, and when the peak plasma levels of acamprosate and the chosen benzodiazepine occur following intramuscular administration, to guide selection of appropriate discrimination testing times.

A drug discrimination behavioral test to determine if rats identify acamprosate as similar to PCP.

Prior to conducting the study, submit the protocol for review. In the protocol, identify what percent response on the PCP lever constitutes full generalization during the acamprosate challenge tests, how percent response will be calculated, and how response rate will be calculated and assessed for significance.

A behavioral study in animals that investigates acamprosate self-administration and the ability of acamprosate to generalize to phenobarbital in drug discrimination studies.

Behavioral studies showing acamprosate potentiation of morphine analgesia and the ability of acamprosate to act as a partial agonist in serotonin systems. Doses of acamprosate to be used in behavioral studies should represent plasma levels of drug that are within the range of plasma levels of drug that will be seen clinically, as well as plasma levels that are 2-3 times greater than therapeutic levels, if this can be done safely.

22. With respect to the acamprosate enteric-coated tablet dissolution specification, provide the following:
- a. Justification for using Method B over Method A.
 - b. Dissolution data from 333 mg enteric-coated "current" formulation tablet lot(s) used in pharmacokinetic studies using the proposed method, Method B (e.g., Lot # 1862 from BE study, etc.).
 - c. Justification for using _____ speed. If available, provide data from other speeds,
 - d. Justification for using pH 6.8. If available, provide data at other pH values, e.g, pH _____
 - e. Justification for proposing _____ when _____
_____ actually measured, or supportive data for the proposed acceptance criterion.
 - f. Justification for proposing 120 minutes as a single time point for the buffer solution. If available, provide data for time-points earlier than 120 minutes, e.g., 30, 60 minutes, etc.

23. DMF [] which is referred to for the drug substance, acamprosate calcium, is not adequate to support NDA 21-431. The issues outlined in the deficiency letter sent to the DMF holder require an adequate response.
24. Provide a clarification of the differences between the information contained in DMF [] (homotaurine) and DMF [] (acamprosate calcium). Consolidate all pertinent information into one document.
25. The following documentation regarding the proposed commercial packages for the drug product is required:
 - a. Letters of authorization (LOAs) allowing reference to the pertinent DMFs for all packaging components []
 - b. Certification that the raw materials of fabrication for the container closure systems (bottles, caps, liners, innerseals, and blister pack materials) comply with the requirements of the current 21 CFR regulations regarding food contact safety.
 - c. Certification that the raw materials of fabrication for the bulk storage bags comply with the requirements of the current 21 CFR regulations regarding food contact safety.
26. Significant payments of other sorts must be disclosed during the time an investigator is carrying out a covered clinical trial and for one year following completion of the study. Submit a financial certification or disclosure statement for the U.S. trial per the requirements of 21 CFR 54.2(f).

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10.2 TEXT STRINGS USED IN LIPHA'S AUDIT OF SAFETY DATA TO IDENTIFY SERIOUS ADVERSE EVENTS

From resubmission section 8.8, page 61-63, addressing action letter deficiency quoted as "point 5."

Point 5: "There is inconsistency in the reporting of serious adverse events (SAEs) in this NDA. Re-examine your entire database and identify and report all cases of SAEs in all acamprosate clinical trials. Provide case report forms and narrative summaries for each case. Include, but do not limit your search terms to: *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, hepatitis, anaphylaxis, agranulocytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, rhabdomyolysis, tumor, birth defect, congenital anomaly.*"

- All events identified as serious adverse events (SAEs) in the original NDA have continued to be considered as SAEs.
- All events not considered "serious" in the original NDA, all "other" events in the worksheet lists, all translations of adverse event-related CRF text fields have been re-examined for the specific text strings shown below (which includes all terms in Point 5, except as noted in the subsections), in the following manner:

Abortion	Coma	Fatal	Necrolysis	Severe
Agranulocytosis	Congenital	Fell	Neutropenia	Significant
Alcohol*	Convulsion	Gast###	Operat	Steven
Anaphyl	Cure#	Hematemesis	Overdose	Stroke
Aplastic	Death##	Hemoptysis	Pancreatitis	Suic
Arrest	Depress	Hemor	Paraly	Surg
Arrhythmia	Detox	Hepat	Poison	Syncope
Append	Died	Hosp	Pregnan	Threat
Ascites	Disability	Important	Pruritus	Transplant
Birth Defect	Disable	Incapacity	Psychosis	Trauma
Bleed**	Drunk	Infarct	Rash	Tumor
Block***	Dysfunction	Intox	Relapse	Varic
Cancer	Enceph	Johnson	Rhabdomyolysis	Varix
Carcinoma	Exfoliation	Major	Rupture	
Cirrhosis	Failure	Malignant	Seizure	
Colitis	Fall	Mellitus	Serious	

* Items related to withdrawal; symptoms secondary to alcohol given no special consideration; ** Only items related to mouth, G-I tract or rectum were considered (nose bleeds, bleeding lips, menstrual bleeding not considered); *** Excluding items related to nasal blockage or partial bundle branch block; # When related to alcohol dependence; ## Of patient only; ### Gast/Gastro (except for events coding to gastritis, dyspepsia, abdominal pain, and diarrhea).

- The investigator description, the coded term as submitted for the original NDA, and the revised coded term have been reviewed for the presence of these strings.
- Each identified event has been reviewed by experienced and medically knowledgeable individuals who have determined whether or not the event fulfills the definition of a serious adverse event.
- Events with only text strings of “depress”, “pruritus”, and “rash” were not reviewed further, unless additionally qualified (e.g., “severe”) or persistently reported.
- Because the events “abdominal pain”, “diarrhea”, and “vomiting” were extremely common in all treatment groups, these events were not specifically included in the search. However, qualifying words were also searched (e.g., “severe”, “hospital”, “incapacity”, “operation”) which would have permitted identification of these events had they, in fact, been serious (e.g., “severe diarrhea”, “hospitalized due to vomiting”).
- For Group I studies:
 - Narratives have been provided for all patients identified as having an SAE, including those in the Follow-up Phase. These can be found in Appendix 8.8.24.13.1A and B, Volumes 21-22, ordered alphabetically, by study, and, within study, by numerical patient order, but without regard to treatment group (treatment group is shown as part of the formatted header).
 - All related CRFs are provided in electronic format, with hyperlinking to translated text fields, where applicable. For each study with the CRF in a foreign language, a translated CRF template is provided as part of the electronic file.
- For Group II-IV studies:
 - Narratives for SAEs for these studies have either been developed from the CRFs, when available (Group IV) or have been copied or written from the study report, using all available information. These are located in Appendices 8.8.24.13.1.2 (Group II), 8.8.24.13.1.3 (Group III) and 8.8.24.13.1.4 (Group IV), Volume 22.
 - When available, related CRFs are provided in electronic format, with hyperlinking to translated text fields, as applicable. For each study with the CRF in a foreign language, a translated template CRF is provided as part of the electronic file.

- For spontaneous post-marketing Pharmacovigilance reports:

A consolidated line-listing has been provided of all reported events from the time Lipha s.a. (now Merck Santé S.A.S.) has been responsible for commercialization of acamprosate. This is located in Appendix 8.8.24.14, Volume 25.

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10.3 MAPPING USED IN LIPHA'S RE-ADJUDICATION OF REASONS FOR PREMATURE DISCONTINUATION

From resubmission Section 8.8, p. 63, the addressing action letter deficiency identified as "point 6":

Point 6: "Examine the reasons for patient discontinuation in order to evaluate the appropriateness of the coding. The reasons for premature discontinuation have been categorized in such a way that some discontinuations due to adverse events or due to lack of efficacy may have been obscured in the category 'other.' Re-code all discontinuations to reflect the reason for withdrawal. Provide case report forms for all discontinuations due to adverse events."

Due to the variety of discontinuation reasons used across the 13 Group I studies, discontinuation reasons for the ISS in the original NDA were grouped into categories of "adverse event", "lost to follow-up", "protocol violation", "treatment failure", "death", and "other". The textual categories as presented in the individual study reports were used to determine the most appropriate category for summary in the original ISS.

In the original ISS, the largest discontinuation category for both the Short-Term studies and the Long-Term studies was "other", which included individual reasons that, when grouped, included "improvement", "investigator decision", "lack of compliance", "patient decision", "sponsor decision", and "other".

In order to provide more precision as to the reasons for premature study discontinuation, the following approach was taken:

- The CRF study termination page or its equivalent was reviewed by experienced and medically knowledgeable persons, blinded to treatment assignments, for all patients in the Group I studies with a discontinuation category of "other" in the original ISS, with particular attention to the possibility that discontinuation might, in fact, have been due to an adverse event.

If "adverse event" or another category was deemed more appropriate, patients were placed in that category on an individual basis in the revised ISS.

- "Patient decision" was added as a category of presentation in the revised ISS and includes individual study categories of "patient decision", "patient refusal", "refusal to continue", "refusal/non-compliance", and "refused medication". If a category other than "patient

decision” was deemed more appropriate upon medical review (again, with attention to the possibility of occurrence of an adverse event as the reason for early termination), patients were placed in that category on an individual basis.

- Reasons for discontinuations in the 3 pivotal Group I studies (Pelc II, Paille and PRAMA) were re-evaluated following a complete translation of text fields of all case report forms and audit of these databases (*see ISE Amendment*).

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Mapping of patient discontinuation reasons in the revised ISS database is as follows:

REVISED ISS CODED REASON	VERBATIM CRF REASON
Adverse Event	Abnormal Laboratory Results Adverse Event Adverse Event/Illness Adverse Events Concomitant Illness Concurrent Illness Intercurrent Med/Psych/Surg Event Severe AE
Death	Death
Lost to Follow-up	Lost to Follow-Up
Other	Improvement Investigator Decision Lack of Compliance No Medication Non-Compliance Other Other Reasons Sponsor Decision
Patient Decision	Patient Decision Patient Refusal Refusal to Continue Refusal/Non-Compliance Refused Medication
Protocol Violation	Protocol Violation Appearance of Exclusion Criteria Exclusion Criteria Concomitant Medication Non-Permitted Medication
Treatment Failure	Treatment Failure Condition Worsened Relapse Severe Relapse Serious Aggravation

Databases have been revised to reflect the above-mentioned changes.

10.4 CLINICALLY SIGNIFICANT CRITERIA FOR LABORATORY TESTS*
Lipha's In-Text Table 8.8.11:2

Lab Test	Units	Low Criterion*	High Criterion	Additional Post-Baseline Criteria
HEMATOLOGY				
Hemoglobin	G/dL	<11.5 (M) <9.5 (F)		Low: low criterion or decrease from Baseline of more than 3 g/dL High: increase from Baseline of more than 3 g/dL
Hematocrit	%	<36 (M) <32 (F)		Low: low criterion or <0.75 x Baseline value
RBC	X10 ⁶ /μL	<LLN	>ULN	
WBC	X10 ³ /μL	<2.8	>16	
Platelets	X10 ³ /μL	<70	>700	
MCV	FL	<70	>105	
Neutrophils	%	≤15		
Eosinophils	%		≥10	
CLINICAL CHEMISTRY				
Total bilirubin	Mg/dL		>2 x ULN	
AST	U/L		>3 x ULN	High: high criterion if Baseline is not clinically significant, >4 x Baseline value if Baseline is clinically significant
ALT	U/L		>3 x ULN	High: high criterion if Baseline is not clinically significant, >4 x Baseline value if Baseline is clinically significant
GGT	U/L		>3 x ULN	
Alkaline phosphatase	U/L		>3 x ULN	
LDH	U/L		>3 x ULN	
Creatinine	Mg/dL			High: >1.33 x Baseline value
BUN	Mg/dL		>2 x ULN	Low: <0.67 x Baseline value High: high criterion if Baseline is ≤ ULN, >3 x Baseline value if Baseline > ULN
Uric Acid	Mg/dL		>1.5 x ULN	High: high criterion if Baseline is ≤ ULN, >2 x Baseline value if Baseline > ULN
Sodium	MEq/L	<0.95 x LLN	>1.05 x ULN	
Potassium	MEq/L	<0.9 x LLN	>6.5	Low: low criterion if Baseline is not clinically significant, <0.9 x Baseline value if Baseline is clinically significant High: high criterion if Baseline is not clinically significant, >1.1 x Baseline value if Baseline is clinically significant
Calcium	Mg/dL	<LLN	>ULN	
Inorganic Phosphorus	Mg/dL	<0.95 x LLN	>1.05 x ULN	
Cholesterol	Mg/dL			High: >2 x Baseline value
Triglycerides	Mg/dL			High: >2 x Baseline value
Glucose	Mg/dL	<50	>250	
URINALYSIS				
Protein				2-step increase on the reagent strip
Glucose				2-step increase on the reagent strip
Casts				Increase from Baseline of at least 2 units for any type of cast
* M = male; F = female; LLN = lower limit of normal; ULN = upper limit of normal.				

10.5 TABLES OF CLINICAL TRIALS

10.5.1 Tabular Summary of Group I Studies: Placebo-Controlled Clinical Trials in the Revised ISS

PLACEBO-CONTROLLED CLINICAL TRIALS ⁶										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
CONTROLLED SHORT-TERM STUDIES										
AOTA/E/91.1 (ADISA) A. Gual, Spain	C (May, 1993 to Oct., 1994)	Volumes 93-96	Pro, MC (11), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS from onset of alcohol withdrawal. (180 days)	Acamp, tabs, 333 mg (#3306)	1998	2 tabs tid	148 ADS (96)	21-61 (41.4)	119/29 (80/20)	ND
				Placebo, tabs (#3305)	6 tabs	2 tabs tid	148 ADS (90)	22-64 (40.6)	117/31 (79/21)	ND

⁶ The following abbreviations are used throughout:

AC = Active comparison	MC = Multicenter	Pro = Prospective
AAS = Alcohol abusing subjects	MD = Multiple dose	R = Randomized
ADS = Alcohol dependent subjects	ND = No data or Not done	RI = Renal-impaired subjects
AC = Acamprosate	NR = Non-randomized	Ret = Retrospective
C = Completed	O = Other	SB = Single blind
CrCl = Creatinine clearance	OE = Over-encapsulated	SC = Single center
DB = Double blind	OL = Open label	S/E = Safety and efficacy
HI = Hepatic-impaired subjects	P = Placebo	SnD = Single dose
HV = Healthy volunteers	PC = Placebo-controlled	WO = Wash-out period
I = Incomplete	PG = Parallel group	XO = Cross-over (number of arms)
LBW = Lean body weight		

⁷ Dates are given as M/D/Y, when available

PLACEBO-CONTROLLED CLINICAL TRIALS ⁴										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA/NL/91.1 AOTA/B/90.2 (BENELUX) P. Geerlings and C. Ansoms, Belgium, The Netherlands	C (May, 1990 to Oct., 1992)	Volumes 90-92	Pro, MC (22), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1519, 3306, 1580 and 3250)	1998 ^{8*} (1332)	2 tabs tid 2-1-1 tabs tid	128 ADS (38)	19-65 (40.3)	97/31 (76/24)	ND
				Placebo, tabs (#1518, 3305, 1579 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	134 ADS (32)	21-63 (41.7)	102/32 (76/24)	ND
AD 04 089 (Ladewig) D. Ladewig, Switzerland	C (Aug., 1989 to Jan., 1991)	Volumes 97-98	Pro, MC (3), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	29 ADS (19)	28-68 (47.7)	25/4 (86/14)	ND
				Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	32 ADS (21)	31-70 (46.9)	22/10 (69/31)	ND

⁸ For studies where acamprosate dose is marked with an asterisk, daily dosage was on the basis of body weight. For patients with a bodyweight greater than 60 kg (or for PRAMA, ≥60 kg): 2 tabs of acamprosate (666 mg) or placebo in the morning, 2 tabs of acamprosate (666 mg) or placebo at midday, and 2 tabs of acamprosate (666 mg) or placebo in the evening (total daily dose of 1998 mg). For patients with a bodyweight less than or equal to 60 kg (or for PRAMA, <60 kg): 2 tabs of acamprosate (666 mg) or placebo in the morning, 1 tab of acamprosate (333 mg) or placebo at midday, and 1 tab of acamprosate (333 mg) or placebo in the evening (total daily dose of 1332 mg). In these same studies, number of patients entered per treatment group and number of patients completing per treatment group are provided for the entire group, irrespective of weight considerations.

PLACEBO-CONTROLLED CLINICAL TRIALS ⁶										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA/B/90.3 (Pelc II) I. Pelc, Belgium, France	C (June, 1990 to April, 1992)	Volumes 76-78	Pro, MC (11), R, DB, PC, PG (3: Groups I vs II vs III; I = acamp, 1332 mg/day, II = acamp, 1998 mg/day & III = placebo) S/E study in ADS, after withdrawal from alcohol. (90 days)	Acamp, tabs, 333 mg (#1624)	Grp. I: 1332 + 2 P tabs	Grp. I: 2 acamp tabs in morning, 1 acamp tab + 1 P tab at midday, 1 acamp tab + 1 P tab in evening	Grp. I: 63 ADS (44)	Grp. I: 21-71 (43.3)	Grp. I: 51/12 (81/19)	ND
				Placebo, tabs (#1623)	Grp. II: 1998	Grp. II: 2 tabs tid	Grp. II: 63 ADS (43)	Grp. II: 26-59 (40.5)	Grp. II 54/9 (86/14)	ND
					Grp. III: 6 P tabs	Grp. III: 2 tabs tid	Grp. III: 62 ADS (32)	Grp. III: 26-59 (40.9)	Grp. III: 55/7 (89/11)	ND
AOTA/I/89.4 (Poldrugo) F. Poldrugo, Italy	C (Oct., 1989 to July, 1992)	Volumes 84-85	Pro, MC (7), R, DB, PC, PG (2: acamp vs placebo) with pre- randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	122 ADS (65)	ND (42.9)	84/38 (69/31)	ND
				Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	124 ADS (47)	ND (44.9)	95/29 (77/23S)	ND
AOTA/I/90.1 (Tempesta) E. Tempesta, Italy	C (Oct., 1989 to April, 1993)	Volumes 86-87	Pro, MC (18), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. (180 days)	Acamp, tabs, 333 mg (#3250)	1998	2 tabs tid	164 ADS (124)	ND (45.9)	139/25 (85/15)	ND
				Placebo, tabs (#3247)	6 tabs	2 tabs tid	166 ADS (122)	ND (46.0)	134/32 (81/19)	ND

PLACEBO-CONTROLLED CLINICAL TRIALS ⁹																	
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics									
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)							
AOTA/LP90/ N001 (UKMAS) J. Chick, United King.	C (June, 1990 to July, 1993)	Volumes 88-89	Pro, MC (20), R, DB, PC, PG (2: acamp vs placebo) S/E study in ADS, after withdrawal from alcohol. A no-treatment period of ≥7 days was to occur between end of alcohol withdrawal and randomization. (24 weeks)	Acamp, tabs, 333 mg (#1624)	1998	2 tabs tid	289 ADS (100)	ND (42.8)	252/37 (87.2/ 12.8)	ND							
				Placebo, tabs (#1623)	6 tabs	2 tabs tid	292 ADS (103)	ND (43.8)	233/59 (79.8/ 20.2)	ND							
ACAMP/US/ 96.1 (US 96.1) B. Mason, United States	C (May, 1997 to Jan., 1999)	Volumes 99-198	Pro, MC (21), R ⁹ , DB, PC, PG (3: acamp 2000 mg vs acamp 3000 mg vs P), with pre-randomization stratification according to alcohol detoxification (yes/no), S/E study in ADS. (6 months)	Acamp, tabs, 500 mg (#3356 and 3570)	Acamp 2000: 2000 + 2 P tabs	Acamp 2000 2 acamp tabs + 1 P tab bid	Acamp 2000: 258 ADS (106)	Acamp 2000: 23-72 (44.9)	Acamp 2000: 176/77 (70/30)	Acamp 2000 217/24/12/0 (86/9/5/0)							
											Placebo, tabs (#3557 and 3569)	Placebo: 6 P tabs	Placebo: 3 tabs bid	Placebo: 260 ADS (143)	Placebo: 22-69 (44.4)	Placebo: 166/91 (65/35)	Placebo: 220/18/11/8 (86/7/4/3)

⁹ Randomization was in a ratio of 3:1:3 for the treatment groups acamp 2000 mg/day, acamp 3000 mg/day and placebo, respectively.

PLACEBO-CONTROLLED CLINICAL TRIALS ⁶										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
CONTROLLED LONG-TERM STUDIES										
AOTA/P/89.1 (Barrias) J.C. Barrias, Portugal	C (Nov., 1989 to Oct., 1992)	Volumes 202-203	Pro, MC (9), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1580)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	150 ADS (86)	21-64 (39.7)	139/11 (93/7)	ND
				Placebo, tabs (#1579)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	152 ADS (83)	23-63 (41.0)	139/13 (91/9)	ND
AA 11 088 (Besson) J. Besson, Switzerland	C (Jan., 1989 to Jan., 1993)	Volumes 204-205	Pro, MC (3), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight and open-label use (yes/no) of Antabuse (disulfiram) as associated therapy, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1243 and 3249)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	61 ADS (19) ¹⁰	25-62 (42.6)	50/11 (82/18)	ND
				Placebo, tabs (#1242 and 3247)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	57 ADS (19)	26-62 (42.6)	43/14 (75/25)	ND

¹⁰ In this study, 24 patients (20 male, 4 female) in the acamprosate treatment group and 24 patients (17 male, 7 female) in the placebo group also received Antabuse®.

PLACEBO-CONTROLLED CLINICAL TRIALS ⁶																	
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics									
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)							
AD 10 089, (Lesch) O. Lesch, Austria	C (Dec., 1989 to March, 1993)	Volumes 199-201	Pro, MC (5), R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, S/E study in ADS, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#1624)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	224 ADS (94)	22-64 (41.9)	168/56 (75/25)	ND							
				Placebo, tabs (#1623)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	224 ADS (85)	15-70 (42.0)	185/39 (83/17)	ND							
544 (Paille) F. Paille, France	C (April, 1989 to Nov., 1992)	Volume 83	Pro, MC (31), R, DB, PC, PG (3: Treatment 1 = P; vs Treatment 2 = acamp, 1332 mg; vs Treatment 3 = acamp, 1998 mg) S/E study in ADS, committed to abstinence, after withdrawal from alcohol. (360 days)	Acamp, tabs, 333 mg (#41319, 41328, 41368)	Trt. 2: 1332 + 2 P tabs	Trt. 2: 2 acamp morning: 1 acamp + 1 P midday; 1 acamp + 1 P evening.	Trt. 2: 188 ADS (85)	Trt. 2: ND (43.7)	Trt. 2: 146/42 (78/22)	Trt. 2: ND							
											Placebo, tabs (#41320)	Trt. 3: 1998	Trt. 3: 2 acamp tabs tid	Trt. 3: 173 ADS (90)	Trt. 3: ND (43.3)	Trt. 3: 137/36 (79/21)	Trt. 3: ND

PLACEBO-CONTROLLED CLINICAL TRIALS ⁴										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ⁷	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA 411.198 (PRAMA) H. Sass, Germany	C (Oct. 16, 1990 to Dec. 3, 1992)	Volumes 79-82	Pro, MC (12), R, DB, PC, PG (2: acamp vs P, with pre-randomization stratification according to body weight) S/E study in ADS, after withdrawal from alcohol. (48 weeks)	Acamp, tabs, 333 mg (#3251)	1998 ^{*20} (1332)	2 tabs tid 2-1-1 tabs tid	136 ADS (79)	21-58 (41.9)	102/34 (75/25)	ND
				Placebo, tabs (#3248)	6 tabs (4 tabs)	2 tabs tid 2-1-1 tabs tid	136 ADS (55)	21-65 (40.5)	109/27 (80/20)	ND

10.5.2 Tabular Summary of Group II Studies: Clinical Pharmacology Studies in the Revised ISS

CLINICAL PHARMACOLOGY STUDIES ¹¹										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ¹²	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Pharmacokinetic/ADME Studies										
HRC/LPA125/8 9391, (Chasseaud) L.F.Chasseaud, France	C (June 29, 1988 to July 28, 1988)	Volume 37	NR, OL, SC, SnD, radio-labeled (³⁵ S), PK study. Blood, urine, & stool samples collected over 120 hours, post- dose. (1 day)	Acamp, radio- labeled (³⁵ S) oral solution, 1320 mg/100 ml (³⁵ S- Acamp: #LPA 125/1) (Acamp: #1814)	1320	SnD solution, 100 ml, fasting	2, HV (2)	34, 37 (ND)	2/0 (100)	2/0/0/0 (100/0)

¹¹ The following abbreviations will be used throughout:

AC = Active comparison	MC = Multicenter	Pro = Prospective
AAS = Alcohol abusing subjects	MD = Multiple dose	R = Randomized
ADS = Alcohol dependent subjects	ND = No data or Not done	RI = Renal-impaired subjects
Acamp = Acamprosate	NR = Non-randomized	Ret = Retrospective
C = Completed	O = Other	SB = Single blind
CrCl = Creatinine clearance	OE = Over-encapsulated	SC = Single center
DB = Double blind	OL = Open label	S/E = Safety and efficacy
HI = Hepatic-impaired subjects	P = Placebo	SnD = Single dose
HV = Healthy volunteers	PC = Placebo-controlled	WO = Wash-out period
I = Incomplete	PG = Parallel group	XO = Cross-over (number of arms)
LBW = Lean body weight		

¹² Dates are given as M/D/Y, when available.

¹³ Numbers of subjects/patients in bold represent the total subject/patient population in each study or unique study group. A total of 522 subjects/patients were enrolled in these 33 studies.

CLINICAL PHARMACOLOGY STUDIES ¹¹										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ¹²	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
IRI 7488, IRI 7646 (Scott) G. Scott, Scotland	C (Nov., 1990)	Volume 37	NR, OL, SC, SnD, radio-labeled (¹⁴ C), PK study. Blood, urine, & stool samples collected over 120 hours, post- dose. (1 day)	Acamp, radio- labeled (14C) oral solution, 6.08 g/115 ml (¹⁴ C- Acamp: #89355) (Acamp: #3011)	1320	SnD solution, 2 hrs after a light standard meal	4, HV (4)	33-41 (36.8)	4/0 (100)	ND
ACAMP/F/ 98.02 (Caplain) H. Caplain, France	C (Sept., 1998 to Dec., 1998)	Volume 38	NR, OL, SC, SnD, one group, IV PK study. Blood & urine were collected for 24 & 72 hrs post-dose, respectively. (1 day)	Acamp, injectable solution, 150 mg/10 ml (#9175)	333	SnD IV infusion over 15 min (fasting)	12, HV (12)	20-38 (25.6)	12/0 (100)	12/0/0 (100/0)
Pharmacodynamic/Pharmacokinetic: Dose/Rising Dose Studies										
Meram ¹⁴ : Oct. 27 1986, (Boismare) F. Boismare, France	C (Feb. 15, 1984 to ?)	Volume 39	NR, SC, OL, 4 part rising dose (3 days at each dose level: total 12 days)	Acamp, capsule, 250 mg (#ND)	750 1500 2250 3000	1 caps tid 2 caps tid X 3 days 3 caps tid X 3 days 4 caps tid X 3 days	10 ¹⁵ HV (10) 10 (8) 8 (8) 8 (7)	ND	10/0 (100/0)	ND

¹⁴ Study does not have an official number (Meram study) and is thus identified by date of study report.

¹⁵ Ten subjects in total in study. All subjects were to receive all doses.