CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-431

Medical Review(s)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthetic, Critical Care, and Addiction Drug Products

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-431
Original NDA Submission Date: 12/21/2001
Complete Response Date: 2/3/2004

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Established Name: Acamprosate Calcium Tablets
Proposed Trade Name: Campral
Sponsor: Lipha Pharmaceuticals, Inc.

Priority Designation: P

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON APPROVABILITY

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 application contains adequate data to characterize the safety profile and to establish that the benefits of acamprosate outweigh the risks in the intended population.

The efficacy of acamprosate in 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.

Approval is recommended.

1.2 RECOMMENDATION ON POST-MARKETING ACTIONS

1.2.1 *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.

1.2.2 Required Phase 4 Commitments

Carcinogenicity studies in mice should be repeated.

1.2.3 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.

[redacted]

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

1.3 SUMMARY OF CLINICAL FINDINGS

Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine. Homotaurine (3-amino-propanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, with structural

similarities to the neurotransmitter, γ-amino butyric acid (GABA). Acamprosate appears to restore balance between the inhibitory transmitter GABA and the excitatory transmitter glutamate, with a major mechanism being the normalization of function of glutamate receptors of the NMDA receptor subtype, thus playing a role in the treatment of alcoholism. Acamprosate is marketed in 31 countries. It was first made available in France in 1989, and Lipha estimates [redacted] patients with alcohol dependence have been treated with acamprosate since that time.

1.3.1 Brief Overview of Clinical Program

Product Name: Acamprosate (calcium acetylaminopropane sulfonate)
Route Of Administration: Oral
Indication: [redacted]

This application contained three pivotal trials, one lasting three months and two lasting roughly a year. In addition, safety data and summaries of efficacy results were provided for 6 additional 6-month studies and 3 one-year studies. In the original submission of this NDA, full safety and efficacy datasets were also provided for the single U.S. study in the clinical program. In all but the U.S. study, the indication studied was the maintenance of abstinence in alcoholics who had completed a formal detoxification program. The U.S. study enrolled individuals who had not been detoxified and sought to evaluate acamprosate's role in promoting abstinence; it was not a successful trial.

The pivotal trials included 375 placebo-treated subjects, 372 subjects treated with the dose regimen of acamprosate now proposed for marketing, and 251 treated with a lower daily dose of acamprosate. In the review of the original submission of this NDA, reviewers were unable to establish the adequacy of the safety exposure due to uncertainty regarding the methods of adverse event ascertainment in the different trials. Only 5 studies (the U.S. study, the two one-year pivotal efficacy studies, and two other 6-month non-pivotal European studies) collected spontaneously reported adverse events exclusively. All other studies used a checklist; however, in this resubmission, the sponsor has clarified that for the majority of these studies, spontaneously reported adverse events were collected at each visit prior to review of the checklist. Although the repeated presentation of the checklist has the potential to influence spontaneous reporting at subsequent visits, the reviewers' concerns that these studies did not routinely record events that were not on the checklist was assuaged by clarifying material provided in the resubmission. The overall safety database therefore appears to be adequate to characterize the adverse event profile of acamprosate.

1.3.2 Efficacy

In three European pivotal efficacy studies, subjects randomized to acamprosate were more likely than subjects randomized to placebo to be assessed by the clinician as abstinent, using either continuous abstinence or intermittent periods of abstinence as the success measure. These measures of efficacy differ from the sponsor's labeling claim, which reports the [redacted]' The method of ascertainment of the number of drinking days in the European studies was insufficiently systematic to allow for precise counting of

number of days drinking or not drinking. Therefore, although the data support the claim that acamprosate is effective in maintaining abstinence in recently-detoxified alcoholics, it is not possible to quantify the effect in terms of specific duration of abstinence. The single U.S. study failed to support the efficacy of acamprosate, and this discrepancy was addressed in a meeting of the Psychopharmacologic Drugs Advisory Committee on May 10, 2002. The recommendation of the Committee was to accept the validity of the European studies (pending inspection), and to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor evidence of efficacy in any particular subgroup. The constrained setting in which evidence of efficacy has been demonstrated in European studies (i.e., only in patients who had completed an inpatient detox) was noted.

The three trials which provided evidence of efficacy were:

- **Protocol AOTA/B/90.3 ("Pelc-II"): "A study of the Activity and Tolerance of Calcium Acetyl Homotaurinate (AOTA-Ca) in Helping to Maintain Abstinence in the Weaned Alcoholic Double-Blind Versus Placebo,"** a 3-month comparison of placebo vs acamprosate at 2 different doses in 189 subjects;
- **Protocol 544 ("Paille"): "A Multicentre Controlled and Double-Blind Comparative Study of the Efficacy of AOTA-Ca Studied at Two Dosages and Placebo Over a 1 Year Period of Treatment. Followed by a 6 Month Post-Treatment Period of Placebo on Alcoholic Patients who were Followed as Outpatients After Withdrawal,"** a comparison of placebo vs. acamprosate at 2 different doses in 538 subjects; and
- **Protocol # AOT 411.198 ("PRAMA"): "Prevention of Relapses in Alcoholics with Acamprosate,"** a 48 week study of acamprosate, dosed by weight, in 272 subjects.

The common endpoint applied (retrospectively) to all three studies was the percent of patients remaining continuously abstinent throughout treatment, because this seemed to be credibly determined and represented a clear clinical benefit. The size of the treatment effect varies across studies and depends on the assumptions made about missing data.

The results of the complete abstinence analysis are shown in the table below for the three pivotal trials. The sponsor's algorithm for abstinence assessment is described in detail below; in brief, for each study, available sources of information including patient and significant other report, blood or breath alcohol, and investigator assessments were used to classify patients as abstinent vs. non abstinent. Those who completed the study without being assessed at any time as non-abstinent were considered continuously abstinent. Patients who were assessed as non-abstinent or who did not complete all study visits were assessed as relapsed. The sponsor's datasets for each study include a field that flags each patient as relapsed or unrelapsed. The term "uncensored" is used by the sponsor to designate the analysis in which any patient who did not complete the study is considered to have relapsed, whether or not a relapse was observed prior to study discontinuation.

For Pelc-II, the values listed here are the proportions of subjects with RELFLAGU = 0. (PE_EFFPT.XPT), representing those patients who were assessed as abstinent at each visit

during the full treatment period, and had a duration of participation of at least 90 days. For Paille, the values listed are the proportions of subjects listed as having a time of continuous abstinence of at least 360 days. The additional 6 months of off-treatment follow-up are not considered here. For PRAMA, the values listed are the numbers of subjects coded as not relapsing in the uncensored analysis (RELFLAGU=0, representing those patients who were assessed as abstinent at each visit and had a duration of participation of at least 48 weeks) who did not have the emergence of GGT or MCV values assessed as "abnormal due to alcohol" during treatment. Note that dosing in this study was assigned based on weight: 1998 mg/day for subjects >60 kg and 1332 mg/day for lighter subjects.

It should be emphasized that, due to the visit schedule, it is theoretically possible for subjects to have relapsed and then reattained abstinence between visits; such subjects, if not providing an accurate self-report, might be assessed as abstinent despite a period of non-abstinence. Therefore, these specific values are likely an overestimate of the numbers of patients who were completely abstinent, but the overestimate is expected to be evenly distributed across treatment arms, rendering the comparison meaningful although the numbers themselves may not be.

		Treatment		
Study	Duration of treatment	Acamprosate 1332 mg/day	Acamprosate 1998 mg/day	Placebo
Pelc-II	90 days	26/63 (41%)	24/63 (38%)	8/62 (13%)
Paille	360 days	20/188 (11%)	20/173 (12%)	10/177 (6%)
PRAMA	48 weeks (336 days)	5/24 (23%)	27/112 (24%)	14/136 (10%)

Table prepared by reviewer using Sponsor's electronic datasets and reviewer's definition as discussed in efficacy section below

Considering all dropouts to have relapsed is a common approach in addiction treatment trials, because the likelihood of dropout is greatly increased by relapse to drug use. However, this is likely to be an overestimate of the relapse rate in dropouts. Because each trial had more dropouts in the placebo arm than in the active treatment arm(s), this analysis introduces some bias toward finding a difference in favor of the drug. However, consistent results on other analyses (e.g. time to first relapse, number of visits at which subjects were assessed as abstinent) provides some reassurance (see review of initial NDA submission). Additional support is provided by several additional studies (of 6 months to 1 year), conducted in various countries, which were submitted without primary datasets for review. The continuous abstinence analysis yielded statistically significant results in favor of acamprosate (as reported in the final study reports) in only two of the six European non-pivotal short-term studies; however, in all studies except one, the rate of complete abstinence was higher in the acamprosate group than in the placebo group. The three long-term (1 year) studies did show statistically significant results in favor of acamprosate (based on the analyses in the respective final study reports) in continuous abstinence, adding support to the findings of the 1-year Paille and PRAMA studies, although it must be noted that one study (Besson) was very small and had a low completion rate and was further complicated by permitted

concomitant disulfiram, and that another (Lesch) had only 5 study visits over a 1-year period.

Although the number of subjects considered successful by definition used in the complete abstinence analysis is small (only 12% in the Paille study), the clinical significance of success as defined in this manner in the longer studies is unquestionable.

Additional support is provided by several additional studies (of 6 months to 1 year), conducted in various European countries, which were submitted without primary datasets for review as part of the original NDA. The continuous abstinence analysis yielded statistically significant results in favor of acamprosate (as reported in the final study reports) in only two of the six European non-pivotal short-term studies; however, in all studies except one, the rate of complete abstinence was higher in the acamprosate group than in the placebo group. The three long-term (1 year) studies did show statistically significant results in favor of acamprosate (based on the analyses in the respective final study reports) in continuous abstinence, adding support to the findings of the 1-year Paille and PRAMA studies, although it must be noted that one study (Besson) was very small and had a low completion rate and was further complicated by permitted concomitant disulfiram, and that another (Lesch) had only 5 study visits over a 1-year period.

No direct comparisons of acamprosate to other anti-dipsotropic agents have been undertaken.

Unresolved efficacy issues center on the applicability of the efficacy findings outside the setting in which the efficacy was demonstrated. As noted above, the single U.S. study failed to demonstrate efficacy. The recommendation of the Psychopharmacologic Drugs Advisory Committee was to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor evidence of efficacy in any particular subgroup. Therefore, it must be concluded that there has been no demonstration that acamprosate is effective in subjects who have not undergone detoxification (as in the European studies), or in subjects who are actively drinking at treatment initiation, or in subjects who abuse multiple substances. Because much of the American target population may fall into one or several of these categories, it is important to note the limitations of the data.

During the review of the initial submission of this NDA, doubts were raised about the data integrity of these efficacy studies. Because the safety databases submitted presented a number of barriers to reviewability, an overall concern regarding data integrity existed. Only two sites were inspected by the Division of Scientific Investigations, and at each of these, although no evidence of fraud was present, some "sloppiness" was observed, such as a subject being classified as abstinent despite elevated blood alcohol levels recorded in the CRF, and a subject being classified as non-abstinent due to "missing data" which was, in fact, present in the CRF. Consequently, the Division and Office Directors, upon review, felt that the data from these efficacy studies should not be relied upon to support the efficacy claim for acamprosate. Initially, Lipha was asked to conduct additional efficacy studies. However, in subsequent negotiations, the Division agreed to allow Lipha to perform a thorough audit of the primary source material for these three pivotal trials, and to accept for

review a resubmission based on this audited data.

The efficacy data presented above represent the conclusions supported by the audited data from the three pivotal efficacy studies.

1.3.3 Safety

1.3.3.1 Safety Database

Safety data of varying detail is available from the various study groupings. Little information is available from Group II and III studies.

The table below illustrates the different assessments collected in various Group I controlled Phase 3 studies. Not reflected in the table is the variability in the specific laboratory assessments performed, their timing and extent. The resubmission has provided additional clarity regarding the appropriate groupings and denominators for each safety analysis, identifying the studies which were included in the various analyses and tabulations.

Table 2.3: Enrollment and Assessments in Phase 3 Studies

Common Name	Total Safety Population (Total Acamprosate-treated)	Daily Acamprosate Dose			Placebo	Study Duration (actual exposure varied greatly)	Adverse Events		Vital Signs[2]	Laboratory Assessments[3]	ECGs post-baseline
		1332 mg	1998/ 2000 mg	3000 mg			Spontaneously Reported	Checklist[1]			
Double-Blind, Placebo-Controlled Short-Term Studies											
US 96.1	601 (341)		258	83	260	6 months (24 weeks)	X		X	X	X
Pelc II	188 (126)	63	63		62	90 days (13 weeks)	X	X[4]	X	X	
Poldrugo	246 (122)	31*	91*		124	180 days (26 weeks)	X	X[4]	[2]	X	
Tempesta	330 (164)		164		166	180 days (26 weeks)	X	X[4]		X	
UKMAS	581 (289)		289		292	24 weeks	X		[2]	X	X
BENELUX	262 (128)	32*	96*		134	180 days (26 weeks)	X	X	[2]	X	
ADISA	295 (147)		147		148	180 days	X		[2]	X	
Ladewig	61 (29)	9*	20*		32	180 days (26 weeks)		X		X	
Total	2564 (1317)	135	1128	83	1218						
Total in short-term studies capturing spontaneous adverse events	2503	126	1108	83	1186						
Total in studies measuring ECGs	1182		547	83	552						

		Daily Acamprosate Dose			Adverse Events			

Common Name	Total Safety Population (Total Acamprosate-treated)	1332 mg	1998/ 2000 mg	3000 mg	Placebo	Study Duration (actual exposure varied greatly)	Spont-aneously Reported	Reported by Checklist[1]	Vital Signs[2]	Labor-atory Assess-ments[3]	ECG[4]
Double-Blind, Placebo-Controlled Long-Term Studies											
PRAMA	272 (136)	24*	112*		136	48 weeks	X		X	X	
Paille	538 (361)	188	173		177	360 days	X		X	X	
Lesch	448 (224)	34*	190*		224	360 days		X	[2]	X	
Barrias	302 (150)	48*	102*		152	360 days	X	X[4]	[2]	X	
Besson	110 (55)	11*	44*		55	360 days	X	X[4]	[2]	X	
Total	1670 (926)	305	621		744						
Total in long-term studies capturing spontaneous adverse events	1222 (702)	271	431		520						
Total in all studies capturing spontaneous adverse events	3789 (2019)	397	1539	83	1706						

* Dosing based on body weight (≤60 kg or >60 kg). Patients with a body weight ≤60 kg who were randomized to the acamprosate group received 1332 mg acamprosate daily. Patients with a body weight >60 mg who were randomized to the acamprosate group received 1998 mg acamprosate daily.
[1]The checklist consisted of a 43-item questionnaire.
[2] Vital sign measurements included at least one of the following: systolic and diastolic blood pressure, heart rate, and body weight. Vital sign data were not included in the ISS database, except for US 96.1, Pelc II, PRAMA, and Paille. Vital sign data for the other European studies were presented only as summaries based on study reports. [3]Specific laboratory values assessed varied by study. [4]Spontaneously reported adverse events were collected prior to checklist review and recorded.

Cardiac effects of acamprosate were assessed in only a subset of the clinical pharmacology studies, and only four of these had ECG's available for centralized, blinded, reevaluation. Only two Group I clinical trials recorded ECG's at any point during treatment, and actual tracings were available for centralized, blinded reevaluation from only one. Altogether, centralized, blinded reading of ECGs was performed on tracings from 248 acamprosate-treated and 112 placebo-treated patients; however, non-clinical data on cardiac conduction are available to supplement this information.

The overall safety database is large, but as noted, the ascertainment of safety findings was inconsistent. Deaths were captured for all studies in Groups I-IV; SAEs were documented for a substantial subset of these. As noted, common non-serious AEs were captured spontaneously in approximately 2000 acamprosate-treated patients. The table below summarizes the safety populations for the various safety parameters.

	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

1.3.3.2 Summary of Safety Findings

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.

1.3.4 Dosing Regimen and Administration

The dosing regimen recommended in the proposed labeling is 333 mg, two tablets t.i.d. Lower doses were studied in earlier development, and two studies incorporating a regimen of 1332 mg/day were submitted with data in support of this application. A dose-response relationship is not clear, as studies had identical results (per reviewer's analysis) for both dose groups. Dose toxicity relationships may be difficult to evaluate, as much of the safety database employed dosing based on weight, assigning the lower dose only to smaller subjects. The single study providing safety information for a higher dose (3000 mg/day, given as three 500 mg tablets (used only in the US study) bid) is the U.S. study, which featured more frequent visits and, perhaps as a consequence, a higher rate of reporting of adverse events for all dose levels.

Dose modification for hepatically impaired patients is not necessary as the drug is not metabolized. Use in the severely renally impaired will be not be recommended, due to the lack of experience in this population, and the potential for dramatic accumulation of acamprosate in renally impaired patients. Dose reduction will be recommended for patients with milder impairment.

1.3.5 Drug-Drug Interactions

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.

1.3.6 Special Populations

Overall, women, the elderly, and minorities were poorly represented in the clinical trials database. Women comprised approximately 20% of the patients in the integrated safety database of Group I studies. Only 212 of 3720[1] subjects in the integrated safety database of studies capturing spontaneous adverse events were over age 60; even fewer were over 65 as most studies excluded such subjects per protocol. Information about race was collected only in the single U.S. study. Therefore, analysis of effects of race on efficacy cannot be conducted (as the trial was not successful) and analysis of effects of race on safety are limited.

No consistent gender differences in effectiveness were identified. Safety analysis (based on sponsor's summaries) by gender shows that some adverse events were more common in women than in men, with some suggestion of treatment-by-gender interaction for diarrhea, which seemed to be more prevalent in the female subjects on acamprosate (20%, vs 15% in males) while the rates in placebo groups (~10%) were similar across genders, and for

[1] The Safety Population for these 11 studies is 3725, but age information was missing for 5 patients (4 BENELUX, 1 Besson).

headache, experienced by 12% of women in the pooled acamprosate group and 16% of women in the placebo group, compared to 10% of men in both major treatment groups.

Subjects over 65 were excluded from the European studies per protocol (although some appear to have been included). Only 6% of subjects in the integrated safety database of studies capturing spontaneous adverse events were >60 years old. Therefore, exposure in this demographic group was small and may represent an area for further exploration. The older subjects experienced higher rates of adverse events reported in several body systems (based on sponsor's summaries), including digestive system and body as a whole. In the >60 age group, diarrhea was reported in 21% of the acamprosate pooled group vs. 14% of the placebo group. In contrast, in the younger subjects, diarrhea was reported in 16% of the acamprosate pooled group vs. 9% in the placebo group.

Information about the race of subjects was collected only in the U.S. study; therefore it is impossible to draw conclusions about effects of race on efficacy. For the small group of black subjects (52/601), larger treatment group differences in favor of placebo (compared to caucasian subjects) were noted in reports of SGOT increased and hyperglycemia. Additional safety information in a broader population representative of U.S. alcoholics may be indicated.

Pediatric data has not been submitted. Lipha has requested a partial waiver of the requirement for pediatric studies, noting that the product is unlikely to be used in a substantial number of patients under age 12. Lipha has requested a deferral of submission of data on pediatric patients 12 and over and plans to submit a pediatric development plan after approval of the application for use in adults. This strategy is acceptable.

Use in pregnancy is possible, but no information is available on the safety of such use. Preclinical findings suggest teratogenicity. The use of alcohol in pregnancy is of known risk to the fetus. Therefore, it is anticipated that at least some clinicians will assess the potential benefits (abstinence from alcohol) as outweighing the risk. Specific evaluation of pregnancy outcomes may therefore be valuable.

No information about the safety profile in renally impaired patients is available. The adverse event experience in hepatically impaired patients was similar to those without hepatic impairment.

CLINICAL REVIEW

2 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

- Drug Established Name: Acamprosate Tablets
- Chemical Name: calcium acetylaminopropane sulfonate
- Proposed Trade Name: Campral
- Drug Class:
- Sponsor's Proposed Indication(s): C

- Dose: 333 mg tablets
- Regimens: 666 mg (two tablets) p.o. t.i.d.
- Age Groups: Adults
  Studies in adolescents deferred to Phase IV
  Studies in children waived

2.2 STATE OF ARMAMENTARIUM FOR INDICATION

Alcoholism is commonly treated with non-pharmacologic psychosocial therapy and/or mutual self-help groups (Alcoholics Anonymous, e.g.). When pharmacologic treatment is used, the usual practice in this country is to combine medication with psychosocial treatment. However, it should be noted that the paucity of pharmacologic options has tended to drive the treatment of alcoholism into the "behavioral health" arena. The availability of effective pharmacologic treatment may be expected to shift the treatment of alcoholism into the primary care venue.

There are two drugs approved for the treatment of alcoholism, disulfiram and naltrexone.

Disulfiram (Antabuse), a DESI drug approved prior to the requirement of evidence of efficacy, works through a mechanism unlikely to be approved by today's standards. Disulfiram interferes with the hepatic oxidation of acetaldehyde resulting in a 5-10 fold increase serum acetaldehyde concentrations and associated dramatically aversive physical symptoms. Disulfiram's efficacy is limited by poor compliance, and it is generally used only in highly motivated individuals or in compulsory treatment settings. In addition, the label notes that "hepatic toxicity including hepatic failure resulting in transplantation or death have been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function."

Naltrexone, approved initially for the blockade of exogenously administered opioids, received supplemental approval for the treatment of alcoholism in 1995. Its efficacy is also

limited by problems with compliance, and its post-approval acceptance has been limited. Naltrexone's label also carries a warning concerning hepatic toxicity.

2.3 AVAILABILITY OF PROPOSED PRODUCT IN THE U.S..

Acamprosate is not marketed in the United States.

2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED AGENTS

There are no pharmacologically related agents.

2.5 PRE-SUBMISSION REGULATORY ACTIVITY

Acamprosate is a synthetic molecule, originally identified by Laboratoires Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. Acamprosate was authorized for marketing in France, for the indication of maintaining abstinence from alcohol post-withdrawal, in 1987 and has been commercially available (as Aotal) there since 1989, in the 333 mg tablet strength. Lipha also markets the acamprosate 333 mg tablets (as Campral) in 38 additional countries. On 6/25/96, Lipha met with the agency in a Pre-IND meeting to discuss plans to seek marketing authorization in the United States. The initial program proposed consisted of a single multi-center efficacy trial using a new (but compositionally proportional) 500 mg tablet, intended to offer a simpler (b.i.d.) regimen with a total daily dose very similar to the labeled dose for the 333 mg tablet (2000 mg as 500 mg, ii p.o. b.i.d. vs 1998 mg as 333 mg ii p.o. t.i.d.). The single U.S. trial was to support the application as a pivotal safety and efficacy trial; two completed European trials using the 333 mg tablet were to be submitted as confirmatory evidence of efficacy. When the U.S. trial failed to demonstrate superiority of acamprosate over placebo, further discussions were held and Lipha elected to submit an application for the 333 mg tablet using the European data as pivotal. The NDA was submitted 12/27/01 and designated a priority review. Upon review, it was identified that the formatting of the safety data submitted precluded even assessment of the adequacy of the exposure to meet ICH standards, and also presented significant barriers to assessment of the overall safety profile. Although concerns about the conflicting results of the efficacy trials were assuaged at a meeting of the Psychopharmacologic Drugs Advisory Committee on 5/1/02, concerns raised during review of the safety data, along with reports of inconsistencies noted during DSI inspections, cast doubt upon the reliability of the submitted data to support efficacy. Taken together with chemistry and pre-clinical deficiencies, the application was deemed "non-approvable" on 6/27/02. Initially, Lipha was asked to conduct at least one additional efficacy study to support the application; however, during subsequent meetings, the Division agreed to accept for review a full re-audit of the pivotal studies, using a common, retrospectively-applied efficacy outcome measure of indisputable clinical significance: the rate of complete abstinence throughout treatment.

Several milestones in the development program are noted in the table below.

6/25/96	Pre-IND meeting	Proposal to study 500 mg tablet (ii p.o. b.i.d) in a single U.S. study, and to submit this plus two completed European studies of 333 mg tablet (ii p.o. t.i.d.) as pivotal. Agreement in principle by Agency.
10/29/96	IND 51,809 opened	
10/27/98	"update" meeting	Need for safety data in polysubstance abusers discussed; sponsor also encouraged to consider geriatric and pediatric issues.
1/27/00	Pre-NDA meeting	US Trial failed to meet primary efficacy endpoint; post-hoc analysis proposed but not accepted by Agency. Plan for NDA revised to current approach of seeking marketing authorization for 333 mg tablet using completed European trials as support.
6/7/00		Letter from NIAAA indicating that there were no concerns about the applicability of European data to the American alcoholic population.
12/27/01	NDA submission	
5/1/02	PDAC Meeting	Discussion of conflicting results of American vs. European studies
6/27/02		Multiple deficiencies were identified including: - issues with in-process controls for both intermediates and final drug product - unsuitable dissolution tolerances - stability-related deficiencies - inadequacies of general toxicology, genetic toxicology, and carcinogenicity programs - inadequacies of safety database precluded assessment of overall extent of exposure, safety experience - insufficiency of evaluation of effect on cardiac conduction - lack of abuse liability information - uncertainty regarding data quality supporting efficacy
10/9/02 3/4/03	Post-Action Meetings	Clarification of data quality concerns; negotiated agreement to accept re-audited data of existing studies using complete abstinence as efficacy outcome.
12/19/03	Response to Non-approval Action Submitted	A listing of the deficiencies identified in the 6/27/02 non-approvable action letter is included in the appendix to this review. Response was deemed incomplete because of lack of adequate table of contents
2/3/04	Complete Response	Table of contents submitted; response deemed complete.

2.6 OTHER RELEVANT BACKGROUND INFORMATION

2.6.1 Foreign Marketing Status

Acamprosate is marketed in authorized for marketing in 39 countries and marketed in 31. It was first made available in France in 1989, and Lipha estimates [ ] patients with alcohol dependence have been treated with acamprosate since that time. However, post-marketing safety information is not available from the early years of marketing. Since Lipha became responsible for pharmacovigilance in 1995, over [ ] have been sold, which the sponsor estimates to equate to [ ] "treatment months." Because of the variability of treatment duration, from weeks to years, Lipha has not estimated the size of the exposed population during the time since 1995. The table below illustrates acamprosate's global regulatory status as of 2/04.

Table 2.6.1 Acamprosate Marketing Status

Brand names of medicinal product (and companies)	Countries	(Registration numbers) and dates	Commercialization dates / status
CAMPRAL (MERCK GmbH WIEN)	AUSTRIA	(1-21427) 25.04.1996	01.07.1996 / marketed
ACAMPROSATE "LIPHA" (MERCK SANTE s.a.s.)		(1-22348) 22.01.1998	Not marketed
CAMPRAL (LIPHA SA)	AUSTRALIA	02.08.1999	10.1999 / marketed
CAMPRAL (MERCK NV)	BELGIUM	(177IS14F3) 29.08.1996	21.04.1997 / marketed
CAMPRAL (INTI BOLIVIA)	BOLIVIA	(003834/99) 10.03.1999	Not marketed
CAMPRAL (MERCK BRAZIL)	BRAZIL	06.10.1998	01.05.2000 / marketed
CAMPRAL (MERCK QUIMICA CHILENA)	CHILE	(F0024/97) 30.09.1997	15.06.1998 / marketed
CAMPRAL (MERCK COLOMBIA S.A.)	COLOMBIA	(007278) 05.11.1997	Not marketed
CAMPRAL (MERCK CENTROAMERICANA)	COSTA RICA	(4116-C2-4646) 12.01.1999	Not marketed
CAMPRAL (MERCK SANTE s.a.s.)	CZECH REPUBLIC	(87/329/98-C) 25.11.1998	01.10.1999 / marketed
CAMPRAL (MERCK SANTE s.a.s.)	DENMARK	(9348) 09.11.1999	03.2000 / marketed

Brand names of medicinal product (and companies)	Countries	(Registration numbers) and dates	Commercialization dates / status
SOBRIAL (MERCK CENTROAMERICANA)	**DOMINICAN REPUBLIC**	(2001-1047) 21.06.2001	Not marketed
CAMPRAL (MERCK ECADOR)	**ECUADOR**	(22.470-11-98) 01.12.1998	11.02.2002 / marketed
AOTAL 333 MG (MERCK LIPHA SANTE s.a.s.)	**FRANCE**	NL 14650 24.07.1987	02.89 by MERAM 27.04.95 by LIPHA SANTE / marketed
CAMPRAL 333 MG (MERCK SANTE s.a.s.)		NL 20245 07.11.1994	Not marketed
CAMPRAL (MERCK SANTE s.a.s.)	**GERMANY**	(34384.00.00) 11.12.1995	15.03.1996 / marketed
CAMPRAL (MERCK GUATEMALA)	**GUATEMALA**	(PF-19,629) 16.03.1998	Not marketed
CAMPRAL (MERCK CENTROAMERICANA)	**HONDURAS**	02.2000	Not marketed
CAMPRAL (MERCK APOTEC Ltd)	**HONG KONG**	(44097) 28.12.1998	Not marketed
CAMPRAL (MERCK HUNGARY)	**HUNGARY**	(OGYI-T-5770) 18.08.1997	15.05.2000 / marketed
CAMPRAL EC (MERCK SANTE s.a.s.)	**IRELAND**	(PA 738/1/1) 16.02.1996	15.07.1996 / marketed
CAMPRAL (BRACCO)	**ITALY**	25.05.1999	Not marketed
CAMPRAL (MERCK NV)	**LUXEMBOURG**	(0923/95/12/0032) 20.12.1995	21.04.1997 / marketed
CAMPRAL (MERCK LIPHA SANTE s.a.s.)	**MAURITIUS**	16.12.1998	Not marketed
CAMPRAL (MERCK MEXICO)	**MEXICO**	(298M99 SSA) 05.07.1999	01.08.2000 / marketed
CAMPRAL (MERCK B.V.)	**NETHERLANDS**	(RVG 18220) 14.11.1995	22.03.1996 / marketed
CAMPRAL (MERCK CENTROAMERICANA)	**NICARAGUA**	(0144321099) 19.10.1999	Not marketed
CAMPRAL (MERCK SANTE s.a.s.)	**NORWAY**	(MT nr 95-1575) 24.06.1997	16.11.1997 / marketed
CAMPRAL (MERCK PERU)	**PERU**	(E-10810) 06.04.1998	Not marketed
CAMPRAL (LIPHA S.A.)	**POLAND**	(7800) 27.07.1998	01.01.2000 / marketed

Brand names of medicinal product (and companies)	Countries	(Registration numbers) and dates	Commercialization dates / status
CAMPRAL (MERCK SANTE s.a.s.)	PORTUGAL	(2409985): box of 60 11.05.1996	11.1997 / marketed
CAMPRAL (MERCK CENTROAMERICANA)	SALVADOR	(F015203021999) 26.03.1999	Not marketed
CAMPRAL (MERCK PTE Ltd)	SINGAPORE	(SIN10890 P) 28.04.1999	01.12.1999 / marketed
CAMPRAL (LIPHA SANTE)	SLOVAKIA	(87/0170/99-S) 28.10.1999	01.01.2000 / marketed
BESOBRIAL (MERCK SOUTH AFRICA)	SOUTH AFRICA	(32/9/0097) 06.02.01	19.03.2001 / marketed
CAMPRAL (MERCK SANTE s.a.s.)	SPAIN	(61.201) 05.12.1996	01.10.1997 / marketed
ZULEX (ALMIRALL)		(61.964) 8.09.1997	01.10.1997 / marketed
CAMPRAL (MERCK SANTE s.a.s.)	SWEDEN	(12698) 13.09.1996	15.05.1997 / marketed
CAMPRAL (MERCK A.G.)	SWITZERLAND	(Nr 53090) 29.08.1995	30.11.1995 / marketed
CAMPRAL (MERCK SANTE s.a.s.)	TURKEY	19.11.2003	01.2004 / marketed
CAMPRAL EC (MERCK SANTE s.a.s.)	UNITED KINGDOM	(PL 13466/0001) 18.12.1995	13.05.1996 / marketed
AOTAL (MERCK VENEZUELA)	VENEZUELA	(E.F.31.040) 03.05.00	11.02. 2002 / marketed

APPEARS THIS WAY
ON ORIGINAL

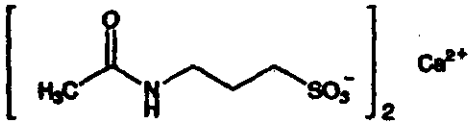
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Much of the material below is taken from the sponsor's NDA summary and was presented in the original review of the NDA.

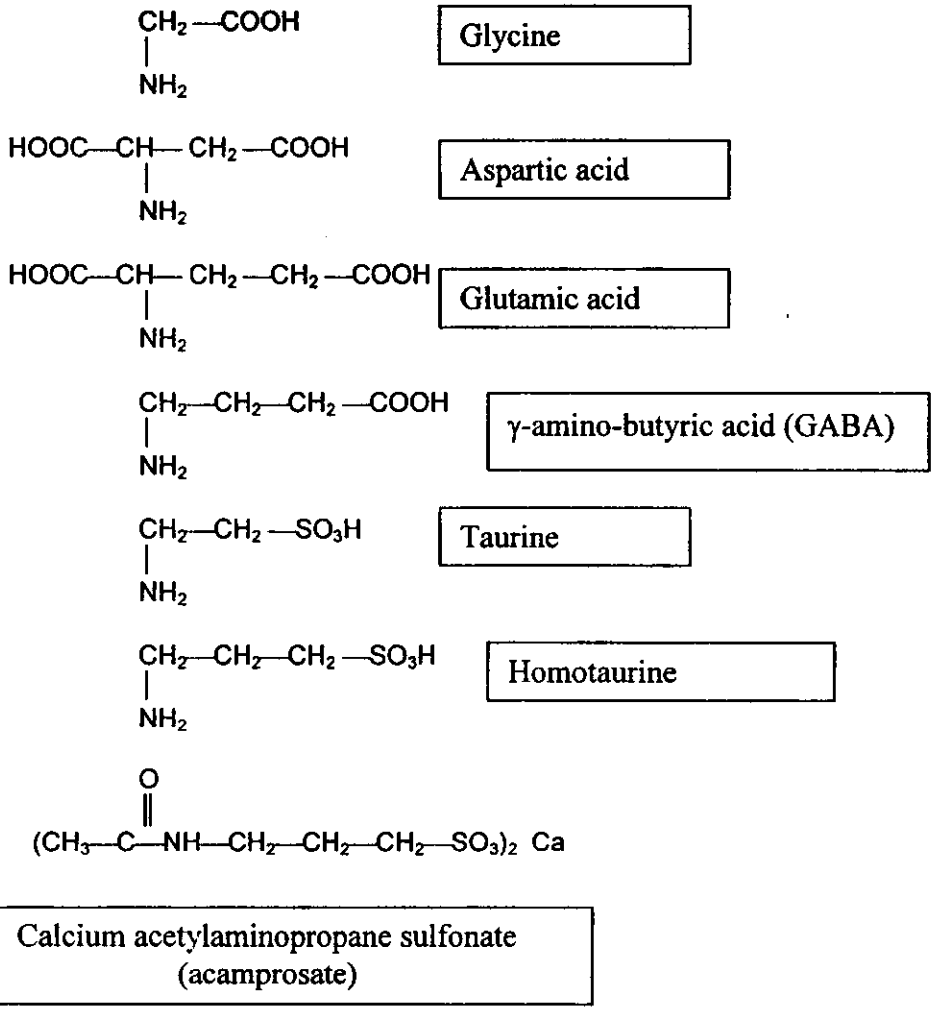
3.1 CHEMISTRY

The chemistry, manufacturing, and controls aspects of this application were reviewed by David Lewis, Ph.D.

The chemical structure of acamprosate is shown below.



The following structures (acamprosate at bottom) illustrate the structural comparison of acamprosate to related molecules.



Acamprosate is synthesized [—] The key intermediate is homotaurine. The product is very stable, with little degradation noted through 36 months.

Campral tablets are enteric-coated. This coating delays release of acamprosate and warrants description of the product as s delayed-release tablet.

The synthesis involves metabisulfide, which should be noted in labeling due to the potential for allergic reactions to residual sulfides.

3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY

(This material is taken from the Pharmacology/Toxicology Review prepared by Drs. Kathleen Haberny and Timothy McGovern at the time of the original NDA review and additional material prepared by Dr. Adam Wasserman during review of this amendment.)

3.2.1 Safety pharmacology

Acamprosate had negligible central nervous system activity except for a slight increase in spontaneous activity in rats and attenuation of induced hyperactivity in mice. No cardiovascular

effects were noted in normal rats, but acamprosate reduced blood pressure in spontaneously hypertensive rats. Cardiovascular effects were minor in dogs, and included slight decreases in heart rate and respiratory rate, and slightly increased PR and QRS intervals when administered intravenously; no effects on QT interval were noted. Oral administration induced sporadic instances of 2nd degree auriculo-ventricular heart block and ventricular premature beat after 13 weeks, but not 26 weeks, of treatment in dogs.

The non-approvable letter sent by the Agency requested the sponsor to conduct *in vitro* studies designed to assess the potential for acamprosate to interact with ion-channel function in cardiac tissue as part of the safety testing requirements for new chemical entities and first-in-class drugs. These studies were conducted for the 2nd cycle of this NDA by the sponsor and a general assessment of cardiac toxicity in *in vitro* and *in vivo* preclinical models exposed to acamprosate with subsequent extrapolation to human safety was also provided. Acamprosate exposure did not produce inhibition of HERG tail current at any concentration tested while negative and positive controls produced the expected response. Exposure of Purkinje fibers to acamprosate at concentrations of 30, 100 or 300 μM did not produce any dose-related changes in APD, MRD, upstroke amplitude or resting membrane voltage at frequencies of 1 or 0.5 Hz. Taken together, these results suggest that acamprosate is not likely to adversely affect voltage-gated K^+ or Na^+ channels of ventricular Purkinje cells at concentrations up to 300 μM.

3.2.2 General toxicology

Studies up to 6-months duration were performed in rats and dogs. In rats, effects on renal function including decreased urinary volume (up to 37%) and significant increases in urine calcium (2-13 fold) were observed in a 3-month oral toxicity study. Other kidney effects included distension of kidney tubule sections from coagulum accumulations attributed to early senile nephrosis in 3/12 animals at the high dose of 2400 mg/kg. In the 6 month study, 22 of 60 animals died between weeks 15 and 26 of dosing at the highest dose (2400 mg/kg). Associated renal lesions in 15 of these animals included vacuolation, calculi, tubular ectasia, pelvic distension, intracellular mineralization and epithelial atrophy. Other target organs included heart (mineralization, myolysis, fibrosis, myocarditis and pericarditis), brain (thrombus, vacuolation) and GI tract (mineralization, hyperkeratosis, dyskeratosis, inflamamtion). Grossly, GI changes included hypertrophy, gas, distension, and liquid contents. Again a 2-20 fold increase in urine calcium was noted. A NOAEL was not identified in this study and was < 320 mg/kg.

In a 6-month dog study, observations included diarrhea, cardiac abnormalities described earlier, increased urinary calcium. No definitive target organs were identified in dogs at doses up to 1000 mg/kg. This was identified as a deficiency during the first cycle review, and Lipha conducted an additional one-month oral toxicology study in dogs at doses of 750, 1500 or 3000 mg/kg/day or placebo for 28 days by oral gavage in an attempt to characterize the toxicity of acamprosate in a non-rodent animal model using a top dose which would produce toxicity or represent the maximum feasible dose. No target organs of toxicity were identified in surviving animals though dose-dependent GI distress, severe at the highest dose, was observed throughout the study and involved primarily multiple daily bouts of vomiting at higher doses and diarrhea throughout the treatment period. No treatment-related effects were observed on hematologic or clinical chemistry parameters. No treatment related effects were observed on cardiac function or conduction parameters, though 2nd degree AV block was observed in 3 animals in the MD

treatment group (none in the HD group); of these, 2/3 animals had evidence of this anomaly within the pre-treatment baseline period. No treatment related changes were noted in organ weights, gross necropsy findings or in a histopathologic evaluation of tissues. Doses utilized represent 10 – 42-fold (body surface area-adjusted for a 50 kg individual) the maximum recommended human dose (MRHD) while systemic (AUC) exposures attained provide a 22 – 81-fold safety margin above human exposure at steady state therapeutic dosing.

3.2.3 Genetic toxicology

Acamprosate was not mutagenic in the Ames test, and was not clastogenic in the Chromosome aberration assay in human lymphocytes and in the in vivo Mouse Micronucleus test. Equivocal findings were observed in a point mutation assay using Chinese hamster V79 cells treated with 100-3000 mg/plate without metabolic activation; results were negative with metabolic activation. However, because of the positive findings, the genotoxic potential of acamprosate could not be ruled out, and the need for additional evaluation was identified as a deficiency during first-cycle review. A repeat of the *in vitro* chromosomal aberration assay in human lymphocytes and the mammalian cell gene mutation assay in Chinese hamster V79/HRPT cells using adequate dosing and current methodology were provided in the current submission and reviewed for this 2nd cycle. No evidence of genotoxicity was identified.

3.2.4 Carcinogencity

Under the conditions tested, acamprosate was not carcinogenic in rats. The study in mice was considered to be inadequate to provide a definitive assessment of the carcinogenic potential. The results of the carcinogenicity studies in mice and rats were presented to the Executive CAC committee on March 19, 2002. The committee concluded that the doses used in the rat study were only marginally adequate based on ICH criteria, but the study can be accepted based on overall toxicity and renal effects, particularly in the male rats. The carcinogenicity study in mice was found unacceptable due to inadequate dose selection, based on lack of evidence for an MTD. In addition, the mouse study results were confounded by nematode infestation and histopathology evaluation was conducted on an inadequate number of low- and mid-dose animals. The committee recommended that the sponsor repeat the mouse carcinogenicity study. This was identified as a deficiency in the non-approvable action letter. However, the sponsor did not repeat the mouse carcinogenicity bioassay, instead electing to submit an expert report reviewing the existing carcinogenicity study along with a 28-day repeat-dose toxicokinetic study in the mouse designed to establish the systemic exposure likely to have been achieved in the original mouse carcinogenicity study. Upon review, the arguments put forth in the expert review did not validate the conclusions of the original mouse study, which did not employ adequate dosing for a valid carcinogenicity assessment. However, given the severity of the clinical condition under treatment and the unmet medical need represented by acamprosate, the Division elected to permit Lipha to complete the carcinogenicity evaluation of acamprosate in the post-marketing period.

3.2.5 Reproductive toxicology

Acamprosate did not affect fertility in mice or rats at doses up to 2400 mg/kg or 1000 mg/kg, respectively. No effects on embryo-fetal development were observed in mice or rabbits at doses up 2400 mg/kg or 1000 mg/kg, respectively. However, developmental effects in rat pups were observed at doses of 300 mg/kg or greater and included malformed iris, retinal dysplasia,

retroesophageal subclavian artery, and hydronephrosis. No effects were noted at the low-dose of 50 mg/kg. In peri- and post-natal studies, an increase in the number of maternal mice delivering still-born offspring and the number of still-born offspring was increased at doses of 960 and 2400 mg/kg. No effects were noted at the low dose of 320 mg/kg or in the study performed in rats up to 2000 mg/kg. The findings summarized above indicate that acamprosate should be classified as a Pregnancy Category C. However, the findings in animals should be considered in relation to known reproductive effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans.

3.2.6 Special toxicology

In a rat study to demonstrate the potential to induce the neurotoxic effect known as the "Olney Lesion", Acamprosate (2000 mg/kg, PO) produced no evidence of neuronal vacuolation, necrosis, or microglia in the retrosplenial and posterior cingulate cortices, measured at 4, 12, and 24 hours after dosing.

3.3 PRE-CLINICAL EFFICACY

Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine.

Homotaurine (3-amino-propanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, with structural similarities to the neurotransmitter, γ-amino butyric acid (GABA). Taurine and GABA are considered to be inhibitory, centrally active amino acids. GABA was identified in the early 1980s as being involved in the CNS actions of alcohol and withdrawal from alcohol. Administration of GABA antagonists potentiates the convulsions of ethanol withdrawal, whereas the agonists or substances that increase GABA levels antagonize alcohol-withdrawal convulsions. Cerebellar GABA concentrations have also been shown to decrease after chronic alcoholization. Homotaurine, a GABA agonist which is not naturally occurring, does not cross the blood-brain barrier; acamprosate has been synthesized to overcome this limitation. In addition, acamprosate has structural similarities to glycine and to the excitatory neurotransmitters, aspartate and glutamate (a precursor of GABA)(Figure 1). Based on structural considerations, interactions of acamprosate with receptors for the major amino acid transmitters, GABA (GABA-A receptors, inhibitory) and glutamate (NMDA receptors, excitatory) have been sought.

Although the precise mechanism of action of acamprosate is still under active investigation, at the cellular level, acamprosate has actions which, generally, but not exclusively, suppress neuronal hyperexcitation. In vitro, acamprosate displaced GABA bound to GABA A and GABA B receptors and in vivo reduced the cerebellar cGMP level, increased the number of GABA uptake sites and transporter affinity, thereby speeding uptake by various cerebral structures. These effects suggest a GABAergic type of activity, although electrophysiological evidence appears to rule out any direct acute interaction of acamprosate with GABA A receptors and there is no evidence of an anxiolytic or hypnotic activity of acamprosate. Other studies on excitatory amino acid transmission indicate that acamprosate antagonizes the excitatory action of

glutamate-like amino acids and attenuates excitatory neurotransmission by increasing glutamate uptake in vitro and in vivo. The most recent evidence suggests that the major central mechanism of acamprosate is via modulation of the NMDA receptor. Here, acamprosate may act as a "partial co-agonist", enhancing activation of the receptor at low levels of activation by endogenous activators, but inhibiting activation when levels of endogenous activators are high (as in alcohol withdrawal). At the molecular level an allosteric interaction with a polyamine binding site on the NMDA receptor complex is the current best explanation for this action of acamprosate.

Lipha hypothesizes that the state of alcohol dependence results in disturbance of the fundamental balance in the brain between the inhibitory transmitter GABA and the excitatory transmitter glutamate. Acamprosate is thought to restore this balance, with a major mechanism being the normalization of function of glutamate receptors of the NMDA receptor subtype.

The initial preclinical studies of acamprosate demonstrated dose-dependent reduction in voluntary ethanol consumption in rodents by the oral and intraperitoneal routes, with an onset of action at approximately 15 days. This effect was observed in ethanol-dependent, but not in non-dependent rats. Acamprosate decreased some effects of ethanol, such as analgesia, hyperactivity or hypoactivity, and staggering, decreased ethanol absorption and elimination in rats, and decreased many of the signs of ethanol withdrawal in mice. The mechanism of action appears to involve alterations in gamma-aminobutyric acid (GABA) transmission and antagonism of excitatory amino acids, perhaps by restoring the inhibition/excitation balance that may be altered by chronic alcohol consumption.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

All of the data in the application are from the development programs of Laboratories Meram and Lipha Pharmaceuticals.

The sponsor has grouped the clinical data as follows:

- **Group I:** These are the double-blind, placebo-controlled clinical trials related to claims of effectiveness. Within this group are the controlled, pivotal efficacy studies and the European and U.S. controlled, supportive efficacy studies.
- **Group II:** Clinical Pharmacology studies.
- **Group III:** Early clinical experience studies.
- **Group IV:** Phase IV, uncontrolled studies related to claims of effectiveness

All Group I studies are double-blind, placebo-controlled studies in alcohol-dependent patients. These include 3 pivotal studies (referred to as *Pelc II, PRAMA, and Paille*) and 10 supportive studies, 7 of which are considered "short-term", because the duration of the Treatment Phase was 6 months or less, and 3 of which are designated "long-term", because the Treatment Phase was 1 year. All studies were conducted in Europe except for the U.S. study, ACAMP/US/96.1. Of these studies, 11 captured spontaneously-reported adverse events.

Only ACAMP/US/96.1 was conducted under IND #51,809. Among the supportive short-term studies, the American study, ACAMP/US/96.1 (US 96.1) is given greater emphasis because it involves a U.S. population and also because of the greater available detail in and relevance of safety information.

The summary of safety information for the NDA focuses on data from the Group I studies and presents additional safety data from all other study groupings, as available. The ISS database collectively consists of data from the 3 double-blind, placebo-controlled pivotal efficacy studies (1 short-term and 2 long-term), the European and US Controlled Short-Term Supportive efficacy studies, and the European Long-Term Supportive efficacy studies (Group I studies). In addition, the sponsor's integrated discussion of safety presents and discusses data from the study reports of clinical pharmacology (Group II) studies, from the study reports of early clinical experience (Group III) studies, and from the study reports of Phase IV European Uncontrolled Short-Term Studies (Group IV) studies, as well as pharmacovigilance information. Raw data and line listings were not available for many of these studies.

Lipha provided case report forms (CRFs) and summaries for all deaths, discontinuations due to adverse events, and serious adverse events in the Group I studies. No case report forms were available for either the Group II or Group III studies. When available, related CRFs for Group IV patients experiencing treatment-emergent SAEs were provided. For Group II-IV studies, narratives for patients experiencing treatment-emergent SAEs either were based on information in the CRF (if available) and, at times, related Adverse Event forms or, when available, were copied from the study report or brief summaries.

4.1.1 Exposure by duration in Group I Studies

The extent of exposure was recalculated to determine whether ICH standards were met. Lipha provided a dataset tabulating both duration of exposure and compliance to study medication, SS_EXPO.XPT. During the first cycle of review, uncertainty about the approach to collection of adverse event information created difficulty in establishing how many of the exposed patients were adequately monitored to form a reliable safety database. In this amendment, information has been provided to clarify that all but two of the Group I studies had an adequate approach to capture of adverse event data. Using the SS_EXPO dataset, patients from these studies were selected, and then those whose compliance was <25% were excluded as providing little meaningful information about drug effects. The data on the remaining subjects was summarized by categorical descriptions of treatment duration by Lipha. Combining data from both short- and long-term studies, the overall exposure was as shown in the table below:

Number of Patients At Least 75% Compliant With Treatment, By Exposure Duration, Studies Capturing Spontaneous Adverse Events

	Acamprosate 1332 mg/day	Acamprosate 1998 mg/2000 mg/day	Acamprosate 3000 mg/day	Placebo
Total	278	1163	67	1233
≤4 weeks	5	76	8	75
4 - ≤8 weeks	22	104	5	115
8 - ≤13 weeks	40	135	6	150
13 - ≤26 weeks	73	495	39	539
26 - ≤39 weeks	13	139	9	156
39 - ≤48 weeks	17	21	0	22
48 - ≤52 weeks	65	134	0	129
>52 weeks	43	59	0	47

If all subjects, regardless of extent of compliance, are included, the exposed population at >52 weeks is 123 (71 on the to-be-marketed dose and an additional 52 at the lower dose).

Because categories selected by Lipha obscure some of the critical time points by grouping together exposures that are *less than or equal to* 26 weeks, and those that are *less than or equal to* 52 weeks, to further clarify extent of exposure, the dataset was queried using the field for weeks of exposure. This analysis revealed that the number of subjects exposed for *at least* 26 weeks was 138 in the acamprosate 1332 mg/day group, 353 in the acamprosate 1998 mg/200 mg/day group, and 9 in the 3000 mg/day group (again, including only participants in studies capturing spontaneous AEs and only subjects at least 75% compliant). Using this approach, the number exposed for at least 52 weeks was 59 in the acamprosate 1998 mg/day group and 43 in the acamprosate 1332 mg/day group, somewhat under the 100 patients required by ICH. However, a substantial number of patients fall into the 48-52 week category, supplementing the long-term exposure. Therefore, the overall exposure appears adequate to characterize the profile of adverse events. Because serious adverse events and deaths were also captured in an additional two Group I studies as well as a large safety database from the Group IV studies, the total exposure also is adequate to exclude events occurring at a rate of at least 1/1000.

4.1.2 Overall Exposure

Varying amounts of information are available from the different study groupings. Deaths appear to be captured with reasonable confidence from Groups I-IV. Serious adverse event information appears to be available from most of these studies as well. Routinely collected adverse event data is available from all but two of the Group I studies. Laboratory data and ECG data are available from a subset of studies. Piecing together the information provided, it appears that the safety populations for the various assessments are:

	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

4.2 TABLES OF CLINICAL STUDIES

Tables of the clinical studies included in the database are provided in the appendix.

4.3 REVIEW STRATEGY

For the review of this amendment, the efficacy review focused on the revised efficacy analysis provided by Lipha based on audited data. Only the three pivotal trials were re-examined for this review cycle. The safety review was conducted essentially *de novo*, as the original safety reviewers were unable to complete the safety assessment with the data submitted.

4.4 DATA QUALITY AND INTEGRITY

Data quality and integrity for this amendment was ensured via a 100% audit and recompilation of datasets by blinded auditors on behalf of Lipha for the three pivotal efficacy studies, as well as re-coding of all safety information from the Group I – Group IV studies to ensure capture of all spontaneously-reported adverse events, identification of all deaths and serious adverse events, and proper categorization of reasons for discontinuation.

The Division of Scientific Investigation inspected two sites during the first review cycle and did not issue a 483. However, as noted in discussions below, concerns about "sloppiness" were verbally raised by the inspector with the review division. It is believed that the 100% audit is adequate to address these issues and that little could be gained by further inspection.

4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES

No concerns regarding GCP adherence were identified during the original review of the application.

4.6 FINANCIAL DISCLOSURE

Partial financial disclosure information was provided in the initial submission for this application and no concerns were identified on review. At agency request, a disclosure statement regarding "significant payments of other sorts" for the U.S. trial was submitted on June 24, 2002, completing the financial disclosure requirements. No such payments to investigators were made, and no concerns regarding conflict of interest were identified on the basis of financial information.

5 CLINICAL PHARMACOLOGY

Initial clinical studies for the European multinational marketing authorization dossier (and other national registration dossiers), carried out by Lipha s.a., and presented in this NDA used a formulation of acamprosate 333 mg enteric-coated tablets that was thereafter modified by Lipha s.a. to meet current international industrial requirements. Since the change in formula, the reformulated tablets have been used in subsequent (Phase IV) studies. This formulation is the enteric-coated tablet which is currently marketed worldwide is proposed for marketing in the U.S.

Bioequivalence could be established for $AUC_{0-\infty}$, but not for C_{max} after single dose administration of 666 mg tablets using the clinical development formulation (reference) and the currently marketed formulation (test). A period effect in that study precluded, however, a definitive conclusion regarding single-dose bioequivalence. An additional reason for the lack of bioequivalence with the single-dose study may be high variability in the pharmacokinetics of acamprosate with oral administration, as assessed with population PK modeling. After administration of 666 mg t.i.d. of the same formulations under steady-state conditions, the formulations were bioequivalent (confidence intervals of the ratios within 0.8 to 1.25) with respect to $AUC_{0-\tau}$, AUC_{0-last} and $AUC_{0-\infty}$ and C_{max}.

The acamprosate 500 mg enteric-coated tablet was also manufactured with the "current formula" and differs from the 333 mg tablet only in proportion of ingredients. The 500 mg tablet strength was, and continues to be, utilized in clinical trials in the United States under IND 51,809.

5.1 PHARMACOKINETICS

Much of the text below is taken from the sponsor's summary of pharmacokinetics.

The oral absolute bioavailability of acamprosate tablets after single-dose administration has been shown to be approximately 11%. After administration of two 333 mg tablets, the C_{max} of approximately 94 ng/ml is reached at T_{max} of 4.5 hours. After multiple-dose administration of 666 mg t.i.d., the C_{max} is approximately 353 ng/ml and steady state is reached within 5 days.

Acamprosate is not protein bound. It does not appear to be metabolized, but is excreted unchanged in urine. Renal clearance is high following either oral or intravenous administration, suggesting a role of tubular secretion.

The $T_{1/2}$ after oral administration of acamprosate tablets is approximately 21 hours. This is attributed to rate-limiting absorption, as the terminal half-life is much shorter after i.v. administration (6 hours) and somewhat shorter after administration of oral solution (14-18 hours).

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 and most clinical trials specifically instructed subjects to take acamprosate with meals.

No gender differences in pharmacokinetics have been identified. Age differences have not been studied.

The sponsor reported that, in a cross-study comparison, acamprosate pharmacokinetics in alcohol-dependent patients, following alcohol withdrawal, treated with acamprosate tablets 666 mg t.i.d for 29 days were comparable to results in healthy volunteers studied by the same analytical laboratory.

Studies in subjects with chronic to acute hepatic impairment were performed after single and repeated doses of acamprosate on a t.i.d schedule. There was no modification of acamprosate pharmacokinetics in mild to moderate hepatic-impaired subjects compared to healthy subjects.

Single-dose studies in renal impairment showed that clearance decreased with decreasing creatinine clearance, while C_{max} was increased and T_{max} and plasma elimination half-life were prolonged in patients with renal impairment. Statistically significant increases were seen in patients with severe renal impairment compared to normal controls. Due to the risk of accumulation, the sponsor recommends acamprosate not be used in renally impaired patients.

Acamprosate had no inducing potential on the cytochrome CYP1A2 and 3A4 systems, and in vitro enzyme inhibition studies suggest that acamprosate does not inhibit in vivo metabolism mediated by cytochrome CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4.

Various interaction studies have been performed with acamprosate, relevant to the treatment of alcohol-dependent patients. There was no significant effect of multiple doses of acamprosate on the pharmacokinetics of a standardized dose of ethanol. In a complementary study, there was no evidence of an effect of ethanol on the pharmacokinetic parameters of a single dose of acamprosate tablets (1332 mg). There was no significant effect of disulfiram on the pharmacokinetic parameters of acamprosate, following multiple daily doses in tablet form of both drugs. There was no significant effect of acamprosate on the kinetics of diazepam (or its major metabolite, nordiazepam), following multiple doses of tablets of both drugs. Likewise, there was no significant effect of diazepam on acamprosate AUC under these conditions. There was no significant effect of acamprosate on the kinetics of imipramine (or its major metabolite, desipramine), when a single dose of imipramine was given after multiple doses of acamprosate tablets. There was no significant effect of acamprosate on the kinetics of naltrexone (or its major metabolite, 6-β-naltrexol), when multiple daily doses of acamprosate and naltrexone tablets were co-administered. Conversely, under these conditions, naltrexone increased the rate and extent of absorption of acamprosate, resulting in a significant increase in acamprosate Cmax (33%) and AUC (about 25%).

5.2 PHARMACODYNAMICS

Studies of the effect of acamprosate on EEG parameters and on performance tasks considered relevant to driving, both alone and in the presence of alcohol, were reported in the application. Most of these studies lack clinical applicability.

5.2.1 Effect of Acamprosate on EEG

5.2.1.1 Poenaru: Electropolygraphic (EPG) Study on the Acute Effects of Ethanol (ETOH) on Sleep in Healthy Volunteers Receiving Calcium Acetylhomotaurinate

This was an open-label, uncontrolled 5 period study of the effects of acamprosate and ethanol, alone and combined, on electropolygraphic recordings of afternoon sleep, sponsored by Laboratoires Meram. The date of the report is Oct. 16, 1986.

The study was conducted at the Neuroendocrinology Laboratory, Department of Human Physiology, Saint-Pères Biomedical Teaching and Research Unit, Paris, France, under the direction of Dr. S. Poenaru.

Subjects were 14 healthy volunteers (7 males, 7 females), age 20-50, without alcohol dependence. Electropolygraphic (EPG) recordings of afternoon sleep were made over a minimum of 120 minutes starting at 14.30 hours on 5 occasions (2 reference recordings served as a single period). The EPG equipment included an electroencephalogram (EEG), electromyography (EMG), electrocardiogram (ECG), and an electro-oculogram (EOG). Vital signs were also recorded. Recordings were obtained at the following time points:

- Two reference recordings on successive days before acamprosate administration (Period 1).
- One recording 50 minutes after administering 40% whiskey, dosed to achieve a blood alcohol level of 0.25 to 0.40 g/l (Period 2).
- One recording on Day 14 of acamprosate dosing, at a daily dose of 1332 mg (two 333 mg tablets in the morning, 1 at midday, and 1 in the evening) (Period 3).
- One recording on Day15 after administration of both acamprosate and a ethanol (Period 4).

Volunteers abstained from other alcohol consumption, as well as from consumption of coffee, tea, caffeinated carbonated drinks or other stimulants.

Blood alcohol levels, obtained 45 minutes after the start of the ingestion of alcohol, ranged from 0.09 – 0.29 g/L. All subjects but one (at 0.09) had BAC above the 0.10 level considered evidence of intoxication in the U.S. Notably, however, 4 of 14 subjects had much lower BACs during the acamprosate/EtOH interaction condition (Period 4) than during the EtOH-only condition (period 2), rendering an evaluation of acamprosate's effects on EtOH-induced changes questionable in these subjects.

Comparison of the different EPG findings showed the following :

As expected, alcohol disrupted sleep patterns, increasing the proportion of intrahypnic waking (IW) and the proportion of stage IA (drowsiness) of non-REM sleep (NREMS), while decreasing Stage III of NREMS (established sleep).

The mean values for period 3 (acamprosate alone) did not differ at a statistically different level from the reference recording in proportions of IW. However, about half the subjects did have

increases in IW comparing period 2 to the reference recording. (Note also that the dose used is lower than the dose proposed for marketing.) For the various stages of sleep, there were no statistically significant differences in group mean values between period 3 and the reference recording. However, about a third of the subjects did show an increase in stage IA sleep and a decrease in Stage III sleep, comparable to that seen in the EtOH condition.

Both mean values and individual values for period 4 suggest that the presence of acamprosate tended to normalize stage IA and to increase stage II of NREMS (light sleep) as compared with alcohol on its own. For about half the subjects, the percentage of IW was lower in the acamprosate + EtOH condition than in the EtOH alone condition (although two of these were subjects whose BAC was lower in the combination condition).

The mean percentage of Stage IV sleep (deep sleep) did not differ significantly between the 4 periods. Large inter-subject variations in rapid-eye-movement sleep (REMS) precluded meaningful comparison across conditions.

The study report concluded that acamprosate 1332 mg/day did not disturb sleep and had a tendency to normalize the sleep abnormalities induced by alcohol. Because the dose is lower than that proposed for marketing (and because the individual results in some cases suggested an effect not seen in group mean comparisons), the claim of lack of effect of acamprosate on sleep architecture is not fully supported. There does appear to be an indication that acamprosate normalizes the effect of alcohol on Stage IA sleep. The clinical significance of this finding is unclear.

5.2.1.2 AFB 06/0081-89 (Hermann): Pharmaco-EEG and Psychometric Study to Assess the Central Nervous Effect of AOTAL in Two Dosages (400 and 800 mg) in Comparison to Diazepam (10 mg) and Placebo in Healthy Male Volunteers

This was a double-blind, placebo- and active-controlled, 4-way crossover study in healthy volunteers which compared the effects of single doses of acamprosate (400 mg or 800 mg) and 10 mg diazepam vs placebo (given in random sequence with 1 week washout between periods) on electroencephalograms and various psychometric tests. The study was conducted in 1989 under the direction of W. M. Hermann, M.D., in Berlin, Germany.

Twenty healthy male volunteers subjects entered the study, with 16 completing all study periods. Electroenchephalographic (EEG) recordings were made under 2 conditions which differed in the degree of activation of the subject: a high activation condition, during which time subjects had to perform a reaction time (RT) task (considered suitable for detecting sedative drug effects) and a low activation condition, during which time no stimulus was presented, but subjects were instructed to stay awake (considered suitable for detecting CNS stimulation). During each period, EEG records were taken prior to drug intake and subsequently 1.5, 3, and 4.5 hours after single oral drug administration at each session. Before and after each EEG recording subjects completed a 100 mm visual analog scale to document tiredness. Psychometric tests included an automated test of calculation and the EWL 60-S adjective check list (pre-, 2, 3.5, and 5 hours after drug intake).

There were no systematic differences between acamprosate and placebo in any of the EEG frequency bands, while diazepam differed significantly from both placebo and acamprosate. Diazepam induced systematic changes in the EEG with a reduction of power in the theta and the 2 alpha frequency bands and an increase of power in the 3 beta bands. There were significant treatment effects on the tiredness rating by visual analogue scale. Diazepam also increased ratings of subjective tiredness, compared to placebo, while acamprosate did not.

Performance in a demanding calculation test was clearly impaired under diazepam, both in total number of attempted tasks as well as number of correctly solved tasks. Both doses of acamprosate also reduced performance at the later time periods (3.5 and 5 hours post-dosing).

The applicability of these findings to the steady-state condition is uncertain, as steady-state Tmax after the recommended dosing regimen is nearly four times the single-dose Tmax after 666 mg (which is higher than the 400 mg dose tested in this study but lower than the 800 mg dose).

5.2.2 Effect of Acamprosate on Performance Tasks Relevant to Driving Ability

5.2.2.1 Moser I: The Effects of Aota-Ca on Performances Relevant to Driving

Moser I (Oct. 19, 1987) was a randomized, double-blind, placebo- and active-controlled, 3-way crossover study in 18 healthy volunteers, comparing the effects of single doses of acamprosate 666 mg, diazepam 10 mg, and placebo (separated by 7-day washout) on psychometric tests relevant to driving. The study was conducted in 1987 under the direction of Dr. Liselotte Moser in Cologne, Germany.

Volunteers received each of the following study drugs on a single occasion, all of which were over-encapsulated so as to appear identical: 666 mg acamprosate (two 333 mg tablets); 10 mg diazepam + 1 placebo tablet; or 2 placebo tablets. At each of the 3 sessions, psychometric testing was performed pre-dosing and exactly 1 hour post-dosing. Because this is substantially prior to Tmax for acamprosate, the results of this study do not seem applicable to the clinical situation (further complicated by the observation that Cmax at steady state is nearly 4x that after a single 666 mg dose) and will not be further described in this review.

5.2.2.2 Moser II: The Effects of Aota-Ca Combined with Alcohol on Performances Relevant to Driving in Healthy Volunteers

This was a randomized, double-blind, placebo- and active-controlled, 3-way crossover study in 24 healthy male volunteers, comparing the effects of alcohol loading in association with single doses of acamprosate, diazepam, and placebo (separated by a 7-day washout period) on psychometric tests relevant to driving. The study was conducted in 1987 under the direction of Dr. Liselotte Moser in Cologne, Germany.

Volunteers received each of the following study drugs on a single occasion, all of which were over-encapsulated so as to appear identical: 666 mg acamprosate (two 333 mg tablets); 10 mg diazepam + 1 placebo tablet; or 2 placebo tablets. Immediately after study medication was administered, subjects began consuming 0.75 g/kg of alcohol, given as neat whiskey (40 vol% alcohol content), over 30 minutes, intended to yield a breath alcohol of 0.57 to 0.59 parts per thousand (at least 3 hours after the last meal and 45 minutes after the end of drinking). Testing began 45 minutes after the end of alcohol drinking, timed to approximate Cmax for alcohol, but

only 1:15 after study medication and therefore well before Tmax of acamprosate (4.5 hr).

In this study, subjects in the acamprosate + EtOH performed no worse than subjects in the EtOH + placebo condition; however it must be noted that subjects were too intoxicated to complete subjective scales or to perform a task requiring standing without swaying for 30 seconds. The lack of an additive effect of acamprosate (prior to Tmax after a single dose) on the impairment seen in extremely intoxicated subjects is of uncertain clinical significance.

APPEARS THIS WAY
ON ORIGINAL

6 INTEGRATED REVIEW OF EFFICACY

6.1 BRIEF STATEMENT OF CONCLUSIONS

After 100% audit by the sponsor and readjudication of patients as continuously abstinent throughout treatment or non-abstinent, the three European pivotal trials were found to demonstrate that subjects randomized to acamprosate 1998 mg/day were more likely than subjects randomized to placebo to be assessed by the clinician as continuously abstinent throughout treatment.

6.2 GENERAL APPROACH TO REVIEW OF THE EFFICACY OF THE DRUG

The three pivotal trials, Pelc-II, Paille, and PRAMA, were reviewed in-depth during the initial review cycle for this IND. The original NDA review provides detailed descriptions of the study designs, and concludes that the study designs were suitable to support the efficacy claims. As explained in the original review, the protocol-specified primary endpoints varied, but a common efficacy endpoint was applied retrospectively by the sponsor. This outcome measure, termed "CAD," or cumulative abstinence duration, was actually a calculation of the percent of time on study subjects were thought to be abstinent from alcohol. However, scrutiny of the protocols, case report forms, and data revealed that the level of detail concerning daily drinking patterns was insufficient to support any conclusions about this outcome measure. Day-by-day drinking data was not collected, and visits were widely spaced, calling into question the validity of calculations based on imputed data. Therefore, the reviewer's analysis emphasized complete abstinence, because binary (yes/no) recall data on drug use is considered more reliable than reconstructed informal recall of daily use over long periods of time.

A complete description of the protocols, assessment of study conduct, and analysis of outcome is documented in the original NDA review. The table below summarizes the basic features of the three pivotal studies.

Table 6.2: Summary of Pivotal Efficacy Studies

Study Name/ Protocol #/ PI/Location/Date	**Design**	**Dosage Form, Regimen, Total Daily Dose**	**Type of Patients, # Entered per Group (# completed), Age range/mean, Gender**
Pelc II (AOTA/B/90.3) I. Pelc, Belgium, France June, 1990 to April, 1992	Prospective, Multi-Center (11), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day) 90 days Seven on-treatment visits at days 8, 15, 30, 45, 60, 75, 90	*A (placebo):* 2 Placebo tabs tid *B (1332 mg/day):* 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) *C (1998 mg/day)* 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg)	Alcohol-dependent subjects after detoxification *A:* 62 entered (32 competed) Age 26-59 (40.9) 89% M /11%F *B:* 63 entered (44 completed) Age 21-71 (43.3) 81% M/19%F *C:* 63 entered (43 completed) Age 26-59 (40.5) 86%M/14%F
Paille (544) F. Paille, France April, 1989 to Nov., 1992	Prospective, Multi-Center (31), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate 1332 mg/day vs Acamprosate 1998 mg/day) 360 days Nine on-on-treatment visits: at monthly intervals x 6 months, then bimonthly x 6 months.	Placebo: 2 placebo tabs tid Trt 2 (Acamprosate 1332 mg/day): 333 mg acamprosate tabs, 2 in morning, 1 acamprosate tab + 1 placebo tab at midday, 1 acamp rosate tab + 1 placebo tab in evening (total 1332 mg) Trt 3 (Acamprosate 1998 mg/day) 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg)	Alcohol-dependent subjects after detoxification Placebo: 177 entered (62 completed) Mean age 42.5 83% M/17%F Acamprosate 1332 mg/day: 188 entered (85 completed)Mean age: 43.7 78%M/22%F Acamprosate 1998 mg/day: 173 entered (90 completed) Mean age: 43.3 79%M/21%F
PRAMA (AOTA 411.198) H. Sass, Germany Oct. 16, 1990 to Dec. 3, 1992	Prospective, Multi-Center (12), Randomized, Double-blind, Placebo Controlled, Parallel Group (Placebo vs Acamprosate with pre-randomization stratification according to body weight) 48 weeks Six on-treatment visits at monthly intervals x 3, then quarterly x 3 to week 48	Acamprosate: ≥60 kg: 333 mg acamprosate tabs, 2 tabs tid (total 1998 mg) <60 kg: 333 mg acamprosate tabs, 2 in morning, 1 at midday, 1 in evening (total 1332 mg) Placebo: ≥60 kg: 2 placebo tabs tid <60 kg: placebo tabs, 2 in morning, 1 at midday, 1 in evening	Alcohol-dependent subjects after detoxification Acamprosate: 136 entered (79 completed) Age: 21-58 (41.9) 75%M/25%F Placebo: 136 entered (55 completed) Age: 21-65 (40.5) 80% M/20%F

Although the original efficacy review concluded that the studies provided evidence of efficacy, the DSI inspection results, although no list of inspectional observations (Form 483) was issued, raised the issue of efficacy data reliability because there were subjects at each site whose status as abstinent/non-abstinent was incorrectly recorded. Furthermore, exploration of the data set also revealed discrepancies between documented blood alcohol levels and assessments of abstinence at sites that were not inspected. Taken together with the multiple deficiencies noted in the preparation of the safety database, the Division and Office was concerned that a pervasive problem of data quality cast doubt on the validity of the efficacy findings.

In the Non-Approvable letter sent June 27, 2002, the Agency noted that "the data submitted in this application are inadequate to establish the efficacy of acamprosate for the treatment of 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." The letter indicated that an additional efficacy study would be needed; however subsequently, the Division agreed to accept for review a fully audited dataset from the existing studies.

For each of the 3 pivotal studies, a complete database audit was conducted by independent and experienced good clinical practice auditors, blinded to treatment assignment, comparing database entries against the CRF and available source documents, mainly laboratory reports. This audit covered all fields of the respective CRFs and included the translation of all text fields and comments by qualified, native-speaking translators. Listings of the electronic databases for each of the 3 pivotal studies were provided to the auditors for comparison with CRFs and source documents. Inconsistent values were corrected according to the CRF/source document; values not previously captured which were found to be present were included among the corrections; listings of the changes (corrections and additions) were created. Textual values were entered into spreadsheets by the native-speaking translators. A listing of all changes to pre-existing variables in the database was provided. This fully audited, translated, and corrected database forms the basis of the sponsor's analyses submitted in this amendment .

During a meeting between Lipha and FDA on March 4, 2003, it was agreed that the primary analysis should be the rate of complete abstinence, with dropouts treated as failures. The Division reemphasized skepticism about calculations based on extensively imputed data, such as the CAD. In order to perform the analysis of the rate of complete abstinence, the patient's status at each visit was derived from the data collected on the CRF.

The rate of complete abstinence is the percent of treated patients in each treatment group who were assessed as abstinent for all planned visits during the treatment phase. The algorithm used to define a patient's abstinence status over the entire treatment period was as follows:

A patient was only considered "abstinent" over the entire treatment period (e.g., Complete Abstinence equals "Yes") if the patient attended every visit of the treatment period and had a status of "abstinent" at every visit of the treatment period.
A patient was considered as "not abstinent" over the entire treatment period (e.g., Complete Abstinence equals "No") if the patient had a status of "not abstinent" at any of the visits during

the treatment period.

A patient's status over the entire treatment period was considered "unknown" (e.g., Complete Abstinence equals "Missing") if the patient had an unknown status at all visits during the treatment period or the patient was considered "abstinent" at some visits and had an "unknown" status at all other visits. Unknown status for an individual visit includes sporadic missing data prior to dropout and visits after a patient dropped out of the treatment phase.

Treatment groups were compared for the rate of complete abstinence using a chi-square test. For the primary analysis of complete abstinence, patients with a status over the entire treatment period of "not abstinent" or "unknown" were treated as failures and compared to the number of patients with a status over the entire treatment period of "abstinent."

A secondary analysis was performed using only the patients whose status over the entire treatment period is either "abstinent" or "not abstinent" and excluding all patients with a status of "unknown".

The algorithms used for establishing whether a patient was coded as abstinent at a particular visit varied by study, based on the specific assessments included in the protocol. Each study-specific algorithm is described below.

6.3 PROTOCOL AOTA/B/90.3 ("PELC-II"): A STUDY OF THE ACTIVITY AND TOLERANCE OF CALCIUM ACETYL HOMOTAURINATE (AOTA-CA) IN HELPING TO MAINTAIN ABSTINENCE IN THE WEANED ALCOHOLIC DOUBLE-BLIND VERSUS PLACEBO

Conducted 6/6/90-4/17/92

6.3.1 Protocol

6.3.1.1 Objective/Rationale

The purpose of the study was to compare the efficacy and safety of 2 dose levels of acamprosate and placebo in maintaining abstinence in weaned alcohol-dependent outpatients over 90 days of treatment.

6.3.1.2 Overall Design

This was a prospective, multicenter (11 centers), randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of 2 dose levels of acamprosate and placebo in alcoholics who had completed inpatient detoxification.

6.3.1.3 Population and Procedures

6.3.1.3.1 Inclusion/Exclusion Criteria

A total of 189 subjects were to be recruited (126 in Belgium and 63 in France).

To be eligible, subjects were required to meet the following criteria:

- Age 18-65
- Weight > 60 kg
- DSM-III diagnosis of alcohol dependence
- "the duration of the disruption must be at least one year"
- Abstinent for at least 5 days
- "Monitored as outpatients"

Subjects were excluded for:

- Pregnancy, or "likely to become pregnant"
- "Associated psychiatric pathology involving the induction of a medicinal treatment during the weaning period or during the follow-up period"
- Significant medical illness (examples included "decompensated diabetes, poorly compensated areterial hypertension, septicemia, active TB, poorly compensated cardiac decompensation, progressive neoplasms")
- Epilepsy (not alcoholic withdrawal seizures)
- Renal insufficiency (Cr > 14 mg/L)
- Hypercalcemia
- "Patients whose condition is incompatible with the conditions of the study"
- "Obvious lack of collaboration with the general weaning treatment"
- Prior treatment with acamprosate

Disallowed concomitant medications included:

- Enzymatic inducers of GGT (other than oral contraceptives)
- Antidepressants (with the exception of amitriptyline "if the mental condition justifies it")
- Neuroleptics
- Barbiturates, meprobamate
- Benzodiazepines "will have to be stopped at least 14 days before the treatment begins, with the exception of benzodiazepines taken for over 3 months before the beginning of the trial which may be continued"
- Valproic acid, carbamazepine
- Disulfiram
- Clonidine
- Clomethiazole ("except during weaning")
- Hypnotics (the exception being Zolpidem (Ambien) allowed over a period of not more than 15 days)

6.3.1.3.2 Procedures

Eligible subjects were to be randomized in blocks of 9 to treatment with:
Group I: Acamprosate 1332 mg (333 mg tablets, 2 qam, 1 at middday, and 1 in the evening, with meals)
Group II: Acamprosate 1998 mg (333 mg tablets, 2 with breakfast, lunch, and dinner)
Group III: Placebo (2 tablets with breakfast, lunch, and dinner)

The protocol allowed for the dose to be reduced (midday dose eliminated) for no more than 7

days in response to adverse events.

Between selection and Day 0, the protocol called for a "drying out cure." The nature of this treatment was not specified in the protocol; it appears that subjects reporting recent abstinence were admissable.

Treatment with Acamprosate or Placebo began on Day 0 continued for 90 days.

Nine study visits were planned: day of selection, day 0, day 8, day 15, day 30, day 45, day 60, day 75 and day 90. This provided for seven on-treatment follow-up study visits.

The following time-and-events table illustrates the planned schedule of assessments:

Table 5.3.1.3.2: Time-and-Events Schedule, Pelc-II

	Selection	D0	D8	D15	D30	D45	D60	D75	D90
Review of inclusion/exclusion criteria	X	X							
Medical History		X							
Physical Exam		X			X		X		X
VS		X	X	X	X	X	X	X	X
Psychiatric History		X							
Ham-D, Ham-A		X			X				X
"Psychosocial Adaptation"	X								
Alcoholism History	X								
MAST	X								
CAGE	X								
Alcohol consumption	X	X	X	X	X	X	X	X	X
Alcohol dependency (inquiry re: subjective need for alcohol)	X	X	X	X	X	X	X	X	X
Observable signs of withdrawal	X	X	X	X	X	X	X	X	X
Urine sample for alcohol	X	X	X	X	X	X	X	X	X
Blood sample for GGT and transaminases	X	X			X		X		X
CBC, Chemistry	X				X		X		X
Adverse Events (spontaneous + questionnaire read aloud)		X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X
Pill count		X	X	X	X	X	X	X	X
Concomitant meds		X	X	X	X	X	X	X	X
Distribution of "monitoring booklet"		X	X	X	X	X	X	X	X

Regarding the collection of alcohol consumption data, the case report form contains fields for "Quantity: Average daily consumption on those days on which the patient drinks. 0= abstinent, 1= drinks a maximum of 5 drinks per day, 2= drinks between 5 and 10 drinks per day, 3= drinks more than 10 drinks per day" It does not indicate how this data is to be collected. Similarly, a field exists for "Frequency: Assessment of average frequency of alcohol consumption (regardless of quantity). 0 = abstinent, 1 = drinks a maximum of twice weekly, 2= drinks more than twice a week but not every day, 3 = drinks every day" Again, the method for collecting this information is not specified. Subjects are given self-assessment booklets at each visit and are apparently to mail in the booklet at the one-week point between visits; however, the CRF contains no fields for this mailed-in information.

A "monitoring booklet" was to be distributed to patients, allowing for the "daily recording and quantification by the patient of nervousness, sleeping disorders, shaking of the hands, and desire for alcohol." The protocol called for the booklet to be returned at each study visit and indicated that it "will be used to monitor the patient." The CRF indicates that subjects were to be

instructed to mail back the first week's booklet at the mid-point between the biweekly visits. The CRF does not contain fields for the data collected in the booklets.

Adverse events were assessed "by the spontaneous collection of the somatic complaints and with the aid of a systematic questionnaire." No specific open-ended probe for adverse events is indicated in the protocol or CRF.

There is no description of any psychosocial therapy to be delivered at study visits or external to the study, nor is the receipt (or lack thereof) of such therapy captured in the case report form.

6.3.1.4 Evaluations/Endpoints

The pre-specified "main criterium of judgement" listed in the protocol was "the consumption of alcohol." No a priori strategy for transforming the data collected into an overall assessment of alcohol consumption was identified.

The following data were used **in this amendment** to determine the patient's drinking status at each visit:

- Frequency of alcohol consumption since the previous visit;
- Quantity of alcohol consumed on those days the patient drank since the previous visit; and
- Urine or blood alcohol.

A patient was considered as "not abstinent" at a given visit if:

- Frequency of alcohol consumption since the previous visit was recorded as one of the following:

1 = drinks a maximum of twice weekly
2 = drinks more than twice a week but not every day
3 = drinks every day;
OR

- Quantity of alcohol consumed on those days the patient drank since the previous visit was recorded as one of the following:

1 = drinks a maximum of 5 drinks per day
2 = drinks between 5 and 10 drinks per day
3 = drinks more than 10 drinks per day;
OR

- Positive indicator of urine alcohol via dipstick or quantity of alcohol in blood or urine ≥0.10 g/L.

A patient was considered as "abstinent" at a given visit if:

- Frequency of alcohol consumption since the previous visit = 0 = abstinent; AND
- Quantity of alcohol consumed on those days the patient drank since the previous visit = 0 = abstinent; AND
- No alcohol detected on urine dipstick or quantity of alcohol in blood or urine <0.10 g/L OR urine and blood alcohol are missing.

A patient's status at a given visit was considered as "unknown" if the patient was not considered "not abstinent" using the algorithm above and:

- Frequency of alcohol consumption since the previous visit = Missing; OR

- Quantity of alcohol consumed on those days the patient drank since the previous visit = Missing.

This differs from the original analysis, in that the main evaluations for abstinence in the final study report were based solely upon the quantity of alcohol consumed.

6.3.2 Results
6.3.2.1 Study Conduct/Outcome
6.3.2.1.1 Subject Characteristics

189 subjects were selected for enrollment. There is no indication of how many were screened in order to enroll 189.

6.3.2.1.1.1 Enrollment by Center
Of the total of 189 patients who were selected to participated, 188 patients were randomized: 125 in the 10 Belgian centers (range 3-37) and 63 in the French center (1 Belgian patient withdrew consent). Sixty-three patients were randomized to acamprosate 1998 mg/day, 63 to acamprosate 1332 mg/day, and 62 to placebo. All patients took at least 1 dose of study medication and are included in the ITT population.

Enrollment by center is described in the original NDA review, Table 5.3.2.1.1.1.

6.3.2.1.1.2 Subject Disposition
The table below illustrates patient disposition and reasons for premature discontinuation, based on the audited data and readjudication of reasons for discontinuation conducted for this amendment. More patients in the placebo group discontinued because of being lost to follow-up (24%) compared to 10% for the acamprosate 1332 mg/day and 13% for the acamprosate 1998 mg/day groups. Otherwise, the reasons for premature discontinuation were similar among treatment groups. No deaths occurred during the treatment phase.

Patient Disposition During Treatment Phase –Pelc II

	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (N=62)
Number of Patients Randomized	n	63	63	62
Number of Patients in the ITT Population	n (%)	63 (100%)	63 (100%)	62 (100%)
Number of Patients Who Completed Treatment Phase	n (%)	44 (70%)	43 (68%)	32 (52%)
Number of Patients Who Discontinued Treatment Phase	n (%)	19 (30%)	20 (32%)	30 (48%)
Reasons for Discontinuation:				
Adverse Event	n (%)	4 (6%)	2 (3%)	4 (6%)
Lost to Follow-up	n (%)	6 (10%)	8 (13%)	15 (24%)
Treatment Failure	n (%)	6 (10%)	9 (14%)	10 (16%)
Death	n (%)	0	0	0
Patient Decision	n (%)	1 (2%)	1 (2%)	1 (2%)
Protocol Violation	n (%)	1 (2%)	0	0
Other	n (%)	1 (2%)	0	0
Data Source: Table 8.7.1.1.1.				

Lipha's In-Text Table 8.7.2.2:2 Note: Percentages are based on the number of patients randomized.

6.3.2.1.2 Demographics

The table below illustrates demographic and baseline characteristics of the 3 treatment groups. Most patients in this study were male (81% to 89% across treatment groups) and the mean age ranged from 40.3 to 43 years.

With respect to alcohol use histories, the mean duration of alcohol dependence ranged from 7.5 years (placebo group) to 10.1 years (acamprosate 1332 mg group). Almost all subjects drank 5 or more standard drinks per drinking day prior to treatment. In the placebo group, relatively more (87%) were in the >10 drinks/day category compared to the other groups (71 – 73%% in the acamprosate groups). More than half (62%) of the patients had previously undergone treatment or detoxification for alcoholism, and the groups were similar with respect to the number of patients with 0-1 previous detoxes (66% in acamprosate 1332 mg group, 65% in acamprosate 1998 mg group, and 63% in placebo group) and the number with 3 or more previous detoxes (24%, 21%, and 24%). Not noted in the table below, but reported by the sponsor, the majority did not attend alcoholism self-help groups. All of the patients in the study had undergone detoxification. Patients who reported drinking or had a positive lab evaluation for alcohol at baseline were considered non-abstinent at baseline. Only one subject in the acamprosate 1998 mg/day group (2%) and three in the placebo group (5%) were non-abstinent at baseline.

Demographic and Baseline Characteristics –Pelc II

Characteristic	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (N=62)
Gender	n	63	63	62
Male	n (%)	51 (81%)	55 (87%)	55 (89%)
Female	n (%)	12 (19%)	8 (13%)	7 (11%)
Age (years)	n	63	63	62
	Mean (SE)	43.0 (1.1)	40.3 (1.0)	40.6 (1.1)
	Min, Max	20, 70	26, 59	26, 59
Age Distribution (years)	n	63	63	62
16-39	n (%)	20 (32%)	33 (52%)	31 (50%)
40-59	n (%)	40 (63%)	30 (48%)	31 (50%)
≥60	n (%)	3 (5%)	0	0
Weight (kg)	n	63	63	62
	Mean (SE)	74.0 (1.5)	71.8 (1.2)	72.1 (1.7)
	Min, Max	58, 122	52, 97	56, 137
Marital Status	n	63	63	62
Married	n (%)	30 (48%)	34 (54%)	29 (47%)
Not married	n (%)	33 (52%)	29 (46%)	33 (53%)
Detoxification Prior to Randomization	n	63	63	62
Yes	n (%)	63 (100%)	63 (100%)	62 (100%)
No	n (%)	0	0	0
Abstinent at Baseline@	n	63	63	62
Yes	n (%)	63 (100%)	62 (98%)	59 (95%)
No	n (%)	0	1 (2%)	3 (5%)
Duration of Alcohol Dependence/Abuse (years)	n	63	63	62
	Mean (SE)	10.1 (1.1)	8.3 (0.9)	7.4 (0.9)
	Min, Max	1, 40	1, 45	1, 35
<10	n (%)	33 (52%)	39 (62%)	43 (69%)
≥10	n (%)	30 (48%)	24 (38%)	19 (31%)
Average Standard Drinks per Day at Study Entry	n	63	63	62
<5	n (%)	1 (2%)	2 (3%)	0
5-10	n (%)	17 (27%)	15 (24%)	8 (13%)
>10	n (%)	45 (71%)	46 (73%)	54 (87%)
Prior Treatment or Detoxes for Alcoholism	n	62	62	62
0	n (%)	23 (37%)	25 (40%)	21 (34%)
1	n (%)	18 (29%)	15 (24%)	18 (29%)
2	n (%)	6 (10%)	9 (15%)	8 (13%)
3	n (%)	4 (6%)	2 (3%)	9 (15%)
>3	n (%)	11 (18%)	11 (18%)	6 (10%)
Data Source: Table 8.7.1.2.1 and Table 8.7.1.3.1				

Lipha's In Text Table 8.7.2.3:1

@ Patients who reported drinking or had a positive lab evaluation for alcohol at Baseline are considered non-abstinent at Baseline

6.3.2.1.3 Drug Exposure

In the Pelc II study, mean duration of exposure to study medication for patients in the placebo group (9.4 weeks) was shorter than the duration of exposure for patients in the acamprosate 1332 mg/day group (10.6 weeks) and the acamprosate 1998 mg/day group (11.2 weeks). This

finding can be attributed to more placebo patients discontinuing within the first 4 weeks. Compliance was similar for the 3 treatment groups (mean values of 96.7% to 100.4% across treatment groups) and a similar percentage (94% to 100%) of patients in all treatment groups were at least 75% compliant.

Drug Exposure –Pelc II

Parameter	Statistic	ACAMP 1332 mg/day (N=63)	ACAMP 1998 mg/day (N=63)	Placebo (n=62)
Duration of Exposure (weeks)	N	63	63	62
	Mean (SE)	10.6 (0.5)	11.2 (0.5)	9.4 (0.6)
	Median	12	12	12
	Min, Max	0, 16	1, 17	1, 16
Exposure by Duration Category (weeks)	N	63	63	62
0 - <4	n (%)	8 (13%)	5 (8%)	13 (21%)
4 - <8	n (%)	6 (10%)	4 (6%)	7 (11%)
8 - <13	n (%)	31 (49%)	35 (56%)	23 (37%)
≥13	n (%)	18 (29%)	19 (30%)	19 (31%)
Compliance (%)	N	55	53	49
	Mean (SE)	97.4 (1.5)	96.7 (1.8)	100.4 (1.6)
	Median	99	99	100
	Min, Max	50, 119	69, 129	76, 129
Number of Patients Who Were ≥75 % Compliant	n (%)	52 (95%)	50 (94%)	49 (100%)
Data Source: Table 8.7.1.4.1				

Lipha's In-Text Table 8.7.2.5:1

Note: Compliance is calculated as the number of study drug tablets taken divided by the number of study drug tablets prescribed times 100.

Note: Percentages for ≥75% compliant are based on the number of patients for whom compliance was calculated.

6.3.3 Efficacy Results

6.3.3.1 Sponsor's Analysis

A patient was considered as "not abstinent" at a given visit if:

- Frequency of alcohol consumption since the previous visit was recorded as one of the following:

1 = drinks a maximum of twice weekly
2 = drinks more than twice a week but not every day
3 = drinks every day;

OR

- Quantity of alcohol consumed on those days the patient drank since the previous visit was recorded as one of the following:

1 = drinks a maximum of 5 drinks per day
2 = drinks between 5 and 10 drinks per day
3 = drinks more than 10 drinks per day;

OR

- Positive indicator of urine alcohol via dipstick or quantity of alcohol in blood or urine ≥0.10 g/L.

A patient was considered as "abstinent" at a given visit if:

- Frequency of alcohol consumption since the previous visit = 0 = abstinent; AND
- Quantity of alcohol consumed on those days the patient drank since the previous visit = 0 = abstinent; AND
- No alcohol detected on urine dipstick or quantity of alcohol in blood or urine <0.10 g/L OR urine and blood alcohol are missing.

A patient's status at a given visit was considered as "unknown" if the patient was not considered "not abstinent" using the algorithm above and:

- Frequency of alcohol consumption since the previous visit = Missing; OR

Quantity of alcohol consumed on those days the patient drank since the previous visit = Missing.

The rate of complete abstinence during the 90-day treatment phase was 41% for the acamprosate 1332 mg/day group, 38% for the acamprosate 1998 mg/day group, and 13% for the placebo group. Patients in the acamprosate 1998 mg/day group had a statistically significantly greater percentage of patients remain abstinent throughout the entire trial compared to patients in the placebo group (p=0.001). In addition, a statistically significantly greater percentage of patients in the acamprosate 1332 mg/day group were abstinent over the entire treatment phase compared to the placebo group (p<0.001).

Lipha also calculated the percent days abstinent using the definition:

$$\text{Percent days abstinent (\%)} = \frac{\text{Total number of days of abstinence x 100}}{\text{Total potential duration of exposure to treatment}}$$

The mean (SE) percent days abstinent was 57.8% (5.3) for the acamprosate 1332 mg/day group, 61.0% (4.8) for the acamprosate 1998 mg/day group, and 36.2% (4.7) for the placebo group. Median values were 67% for both the acamprosate 1332 mg/day and acamprosate 1998 mg/day groups, compared to 29% for the placebo group. The percent days abstinent for the acamprosate 1998 mg/day and acamprosate 1332 mg/day groups were statistically significantly greater than that of the placebo group (p<0.001). The difference in percent days abstinent between the 2 acamprosate groups was not statistically significant (p=0.907).

However, the Division's position concerning the reliability of day-by-day drinking data needed to calculate this value has been clearly and consistently expressed. The Division believes that the level of detail available in the data does not support this calculation.

Lipha also calculated a time to first drink and compared this across groups. The median time to first drink calculated from the uncensored approach was 52.5 days for the acamprosate 1332 mg/day group, 52.5 days for the acamprosate 1998 mg/day group, and 17.0 days for the placebo group (see also In-Text Figure 8.7.2.7.2:1). These results demonstrated a prolongation of the median time to first drink for patients treated with acamprosate 1998 mg/day of 3.1 times that for patients treated with placebo. The acamprosate 1998 mg/day and acamprosate 1332 mg/day groups had statistically significantly longer durations of time to first drink compared to the placebo group (p<0.001. The Division has also pointed out that a calculation of

time to first drink which relies upon imputation of a precise day upon which drinking began may not be supported by the data.

6.3.3.2 Reviewer's Analysis

Using the dataset EFFPT_PE.XPT, the sponsor's calculation of the rate of complete abstinence was confirmed. The number of patients who were not flagged as relapsing (RELFLAGU=0) was as shown in the table below:

Rate of Complete Abstinence Throughout Treatment – PelcII

Treatment		
Acamprosate 1332 mg/day	Acamprosate 1998 mg/day	Placebo
26/63 (41%)	24/63 (38%)	8/62 (13%)

Compared to the results calculated on the original dataset submitted to the NDA, this represents re-classification of 2 patients in the acamprosate 1998 mg/day group and one patient in the placebo group from abstinent to non-abstinent.

6.3.3.3 Efficacy Conclusion: Study Pelc-II

Based on reviewer replication of the sponsor's analysis, Pelc-II provides evidence of efficacy of acamprosate in maintaining abstinence in recently-detoxified alcoholics for a period of 90 days.