CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-431

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-431	Resubmission Date(s): 7/23/03; 12/19/03; 1/26/04
Brand Name	U.S.: Campral France: Aotal® World wide: Campral®
Generic Name	Calcium-acamprosate (acetylhomotaurine)
Primary Reviewer	David Lee
Secondary Reviewer	Suresh Doddapaneni
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	Lipha Pharmaceuticals, Inc.
Relevant IND(s)	51,809
Formulation; Strength(s)	333 mg enteric-coated tablet
Proposed Indication	[ ]
Proposed Dosage Regimen	Two 333 mg enteric-coated tablets three times daily

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the responses to the non-approvable letter dated 6/27/02 for NDA 21-431 (acamprosate enteric-coated tablet) originally submitted on December 21, 2001. Overall, the information contained in the responses is acceptable provided that a mutually acceptable language in the package insert can be worked out between the Agency and sponsor and the sponsor commits to resolve the following issue as phase IV commitment;

1. Appropriate dosing information should be developed in severely impaired renal patients.

BACKGROUND

Lipha has responded to Agency's non-approvable letter dated 6/27/02. From Clinical Pharmacology and Biopharmaceutics (CPB) point of view, there were 4 issues, #14-16, and #22, listed in the letter. Listed below are the CPB issues in the letter, Applicant's responses in quotes, and this reviewer's comments. Overall, the Applicant proposes to address the items with proposing appropriate wording in the Package Insert:

DISCUSSION

Item #14:

Since acamprosate is renally cleared, it can accumulate significantly in patients with moderate or severe renal impairment when a dosage regimen of 666 mg three times daily is used. Provide pharmacokinetic data on an appropriately adjusted dosage regimen for these patients that would result in plasma levels comparable to those seen in patients with normal renal function.

Applicant's Response:

The Applicant wishes to address this item with a proper wording in the Package Insert. The following paragraphs are proposed:

> "In the revised Package Insert, Special Populations section, Renal Impairment subsection, the following labeling is proposed:
>
> 'Peak plasma concentrations after administration of a single dose of 2 x 333 mg tablets to patients with moderate or severe renal impairment were about 2-fold and 4-fold higher, respectively, compared to healthy subjects. [redacted]
>
> Patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) [redacted] not be given TRADENAME® (see also CONTRAINDICATIONS).' "

Reviewer's comment:

The Applicant's overall proposal is acceptable. It is noted that no additional pharmacokinetic data were submitted in this response.

With respect to moderate renal impairment, the Applicant's proposal is same as that of the Dr. Haidar's (pharmacometrician) recommendation previously made in the original NDA review (see CPB review dated 6/10/2002).

With respect to severe renal impairment, the Applicant is proposing to contraindicate in this population. The Applicant's proposal is acceptable, however, from the Agency's viewpoint that appropriate acamprosate dosing information may be needed in this population, due to the fact that acamprosate may be useful in severe renal impairment subjects, including elderly, who are alcohol dependent. It is noted that modeling simulation showed unpredictable profiles in this group.

The Applicant should obtain appropriate dosing information in severe renal impairment subjects as a Phase IV commitment. Additionally, the Dosage and Administration section of the Label should be modified accordingly:

[

]

Item #15:

Provide comparative pharmacokinetic data in elderly subjects relative to young adults, since renal function is diminished in this subgroup, resulting in the potential for significant accumulation of acamprosate, if warranted, based on the results of these date, propose an appropriately adjusted dosage regimen.

Applicant's Response:

The Applicant wishes to address this item with a proper wording in the Package Insert. The following paragraphs are proposed:

> "In the revised Package Insert, Special Populations section, Age subsection, the following labeling is proposed:
>
> 'The pharmacokinetics of TRADENAME® have not been evaluated in a geriatric population.' "

Reviewer's comment:

The Applicant's proposal is acceptable. It is recommended that the following paragraph should be added to the proposed wording:

> "Since renal function diminishes in elderly and acamprosate is excreted unchanged in urine, acamprosate plasma concentrations are most likely to be higher in elderly population compared to younger adults. [

]

Additionally, the following paragraph should be added in the Precautions Section of the Package Insert:

[

]

Item #16:

Provide pharmacokinetic data on the effect of disulfiram on the pharmacokinetics of acamprosate.

Applicant's Response:

In the July 23, 2003 NDA Amendment the Applicant has submitted the information on the effect of disulfiram on the kinetics of acamprosate. The Applicant also stated that the theoretical likelihood of such an interaction seems remote, due to the totally different metabolism of the 2 drugs following oral administration. Additionally, the Applicant described the safety profile of acamprosate administered with or without disulfiram. The Applicant stated that the safety profile in subjects administered both acamprosate and disulfiram was not different from the safety profile obtained after administration of acamprosate alone.

Reviewer's comment:

The Applicant's response is adequate. Additionally, the *in vitro* data submitted in the original NDA supports this information. The in vitro data showed that acamprosate did not induce CYP1A2 and 3A4 in human hepatocytes (10 and 100 μM). Acamprosate also did not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 in human microsomes (10 and 100 μM). The in vivo metabolism study showed that acamprosate is excreted as a parent compound via the kidneys. Thus, it is not likely that disulfiram and acamprosate will interact with each other.

Item #22:
With respect to the acamprosate enteric-coated tablet dissolution specification, provide the following:

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

Applicant's Response:

The responses to this deficiency were provided in the NDA 21-431 amendment dated October 23rd, 2003 (pp. 4-31), under the CMC section.

Reviewer's comment:

The following review excerpts are from the CMC Review. Dr. D. Lewis comments that 5 of the 6 responses regarding dissolution specification are adequate, except, sub-item # e). This reviewer concurs with Dr. Lewis' recommendation.

Dr. Lewis's review:

a. **Provide Justification for using dissolution Method "B" over Method "A"**

[ ]

Evaluation: ***Adequate.*** Dissolution method "A" is not proposed for use in the NDA drug product, and is not relevant to the proposed U.S. application.

b. **Provide dissolution data from the 333-mg enteric coated "current" formulation tablet lots used in the PK studies using the proposed dissolution method "B".**

RESPONSE: *October 23rd, 2003 amendment, p. 5.* The batches used in the PK studies for the European registration were tested using the old dissolution method "A" (manufacture and testing was done in 1992). Dissolution method "B" was not developed until 1999. Since the PK batches were manufactured more than 10 years ago, there are no tablet samples available for retesting via method "B".
Evaluation: ***Adequate.*** The lots in question are more than 7 years beyond the proposed expiry, and even if they were available, would not generate any relevant dissolution data. The dissolution test and criteria are judged on the basis of the application of dissolution method "B" to the exhibit (primary stability) batches of CAMPRAL.

c. **Provide justification for using [ ] speed. If available, provide data for other speeds, [ ]**

RESPONSE: *October 23rd, 2003 amendment, pp. 6-7.* A study was performed on 3 industrial batches of acamprosate (1500, 1501, and 1502), to examine [ ] speed. These batches were tested using dissolution method "B" using [ ] speeds. The data is provided in Table 1 (page 6 of the CMC responses):

Comments and evaluation: ***Adequate.*** The regulatory acceptance criterion for dissolution (buffer phase) is [ ] (Q) in 120 minutes. The use of [ ] The use of [ ] with [ ] would have [ ] three exhibit batches (1500, 1501, and 1502). This data was obtained at release. The accumulated comparative data supports the use of [ ] apparatus as being more suitable for the drug product than [ ]

d. **Provide justification for using pH 6.8. If available, provide data at other pH values, e.g., pH**

RESPONSE: *October 23rd, 2003 amendment, pp. 8-9.* The regulatory method pH (6.8) was chosen, based on the recommendations of USP Section <724>. In addition, the influence of pH was initially studied in order to reduce the coating dissolution time, as follows:

[ ] produced a coating dissolution time of [ ]
[ ] produced a coating dissolution time of [ ]
[ ] produced a coating dissolution time of [ ]
[ ] produced a coating dissolution time of [ ]

The selected buffer was [ ] (pH 6.8). Studies were done on [ ] medium (see Figure 2 for multi-point dissolution table):

Comments and evaluation: ***Adequate.*** The acceptance criteria for dissolution are [ ] % in 120 minutes (pH 6.8 buffer). The pH [ ] dissolution profile indicates that the drug product would likely fail this qualification level. The pH 6.8 profile indicates a dissolution level of [ ] % at 120 minutes. The combination of a pH 6.8 buffer and the acceptance criteria of [ ] % in 120 minutes (pH 6.8 buffer) are adequate, as the method is discriminating.

e. **Provide justification for proposing [ ] release [ ] when [ ], is actually measured, or supportive data for the proposed acceptance criterion of [ ].**

RESPONSE: *October 23rd, 2003 amendment, p. 10.* On the basis of current supportive ICH stability data, the sponsor found a maximum value of [ ] and propose tightening the acceptance criterion to [ ] release at [ ] acid stage dissolution.

Comments and evaluation: ***Not adequate.*** The purpose of an enteric-coated solid oral dosage form is to limit the amount of drug substance released in the stomach. The proposed acceptance criterion of [ ] is not supported by accumulated data, which indicates that the maximum recorded value for the determination of acamprosate calcium in [ ] and most of the recorded values were listed as "not detected". A tighter acceptance criterion should be applied to dissolution in acid medium; this criterion should be derived from analytical data. In order to compile statistics on acid-medium dissolution, the limits of detection and quantitation for acamprosate in acidic dissolution medium should be provided. All values of "not detected" should be treated as corresponding to the validated LOD (limit of detection) quantity of acamprosate. The acceptance criterion for release of acamprosate in acid medium should be based on the mean value and standard deviation of the determination of drug substance in acid medium utilizing the LOD concentration level.

Request for information (deficiency): Provide the LOD and LOQ (limits of detection and quantitation) for determining acamprosate sodium in acid medium. Calculate the mean, standard deviation, and mean plus 3 sigma, in which all values listed as "not detected" are treated as the LOD concentrations for these calculations (*e.g.*, if the LOD was determined to be [ ] all values listed as "not detected" should be entered into the calculations as [ ]. The acceptance criterion for acamprosate sodium release at [ ] in acid solution should be based on the data, to be calculated as requested above, and should correspond to the mean determination plus three sigma.

f. **Provide justification for proposing 120 minutes as a single time point for the buffer solution. If available, provide data for time-points earlier than 120 minutes, *e.g.*, 30, 60 minutes, etc.**

RESPONSE: *October 23rd, 2003 amendment, pp. 11-30.* Complete dissolution data [ ] are available for stability samples (lots 1500, 1501, and 1502 in blisters, bottles, and bulk packaging).

Comments and evaluation: ***Adequate.*** The proposed regulatory acceptance criteria (tolerances) for dissolution, NLT [ ] (Q) in 120 minutes are supported by the accumulated release and stability data. *An alternate tolerance, NLT [ ] (Q) in [ ] minutes would also be supported by the accumulated data.* The only difference between the single-point results obtained at [ ] 120 minutes is that the [ ] test results would occasionally require S2 testing to pass the specifications. However, the drug product does not seem to degrade during stability regarding dissolution test results, so a slightly more discriminating tolerance (*e.g.*, NLT [ ]% in [ ] would not add significant value to the control of drug product quality and potency assurance. The proposed single-point dissolution testing (120 minutes) is adequate for the drug product.

LABELING COMMENTS

The proposed label has been reviewed and modified accordingly using ~~strikeouts~~, and insertions of recommended wording. Additionally, the reviewer's comments are in red text. A dosage adjustment for subjects with insufficient renal function is included in the Dosage and Administration section.

CLINICAL PHARMACOLOGY

Pharmacodynamics

[ ]

Pharmacodynamic studies have shown that acamprosate calcium reduces alcohol intake in alcohol-dependent animals in a dose dependant manner and that this effect appears to be specific to alcohol and the mechanisms of alcohol dependence.

[

]

Comment: Per MO's recommendation

5 page(s)
of draft labeling
redacted from the
approval package

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lee
7/12/04 03:44:06 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/13/04 07:25:19 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-431	Submission Date(s): 12/27/01
Brand Name	U.S.: To-Be-Determined
	France: Aotal®
	World wide: Campral®
Generic Name	Calcium-acamprosate (acetylhomotaurine)
Primary Reviewer	David Lee
Secondary Reviewer	Suresh Doddapaneni
Pharmacometrics Reviewer	Sam Haidar
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	Lipha Pharmaceuticals, Inc.
Relevant IND(s)	51,809
Submission Type; Code	1P
Formulation; Strength(s)	333 mg enteric-coated tablet
Proposed Indication	[ ]
Proposed Dosage Regimen	Two 333 mg enteric-coated tablets three times daily

1 Executive Summary

Lipha has submitted a New Drug Application, NDA 21-431, and is seeking approval for acamprosate enteric-coated tablets, for the indication [ ]

In the submission, the Applicant stated that acamprosate has been commercially available in France since 1989, as Aotal®. Aotal® was initially marketed as 1332 mg/day in divided doses for 3 months treatment in 1989, and, was marketed as 1998 mg/day for 1 year treatment in 1995 (labeling change). Acamprosate (acetylhomotaurine) has since been approved in 38 additional countries. From the submission the following items were identified;

Exposure-response relationship

Regarding acamprosate exposure-response information the Applicant stated that it is difficult to define a exposure-response curve for drugs used in a disease such as alcohol dependence "which lacks clear-cut, universally accepted biological or physiological endpoints which can be accurately monitored." In order to elaborate on this issue the Applicant stated that in the past some of the surrogate or biological markers used in order to assess recent and chronic excessive drinking were elevation of gamma-glutamyl

transferase (GGT), carbohydrate deficient transferrin (CDT) levels and elevation of mean corpuscular volume (MCV) of red blood cells, elevated liver enzymes including GGT, respectively; however, these were taken as supportive evidence measurements. Additionally, the clinician's global assessment of the patient's improvement has been used as an endpoint, and, mostly it is a combination of these assessments which allows judgment to be made as to whether or no the patient is continuing to drink and whether or not there has been improvements. The Applicant's approach was to use the endpoint of cumulative abstinence duration (CAD), either in absolute terms or as a percentage of the amount of time on study (corrected CAD). The current submission appears not to contain acamprosate exposure-response information. The majority of studies including the pivotal studies utilized 1998 mg/day dose.

In the current submission the Applicant stated that two studies of the 3 efficacy studies (Pelc II and Paille) have looked at 2 parallel dose groups of acamprosate (1332 mg/day and 1998 mg/day. The duration of studies was 90 days and 360 days for Pelc II and Paille, respectively. The third efficacy study (PRAMA) was conducted at the total daily dose of 1998 mg. The duration of this study was 48 weeks or 336 days. The Applicant reported that results from the studies seem to indicate that there was no strong evidence of 1332 mg/day leading to effectiveness, however, 1998 mg/day dose was effective. It is interesting to note that, according to the medical officer who assessed acamprosate safety in the current submission, France government authority requested the Applicant to study the effectiveness of 1998 mg/day regimen after the initial acamprosate approval in 1989. From a safety perspective, the Applicant reported that there seems to be increase in GI AE events (especially diarrhea) with increase in dose from 1332 to 1998 mg/daily, however, doses were well tolerated. Additionally, a dose ranging study performed in 1988 of multiple doses of acamprosate tablets, given twice daily, suggested an increase in AE at or above a total daily dose of 2664 mg/day. This study (Dewland I) was a dose ranging study exploring from 666 to 5328 mg daily in two divided doses for 14 days. From the overall information presented in the submission, it seems likely that 1998 mg/day dose may be adequate for the treatment for maintenance of abstinence from alcohol in patients with alcohol dependence.

Enteric-coated formulation and bioequivalence information

Pertaining to the enteric-coated tablet formulation for acamprosate, the Applicant stated that acamprosate was originally studied in capsules given three times daily with total daily doses ranging from 750 mg to 3000 mg. The Applicant reported that in these early studies there was an increased frequency, but not severity, of gastrointestinal (GI) side-effects with total daily doses above 1500 mg/day. Thus, the Applicant explored the enteric-coated table formulation in order to decrease the GI side-effects.

Bioequivalence information

After single dose, only acamprosate AUC was bioequivalent between initial and currently marketed formulations. The Cmax values for point estimate and C.I. were 0.744 and 0.607 – 0.911, respectively.

However, at steady state, the current marketed formulation of acamprosate tablets is bioequivalent to the initial formulation with respect to both C_{max} and AUC.

Overall clinical information and Dosage adjustment information

Acamprosate binds to plasma proteins minimally. Acamprosate appears not to undergo metabolism processes, and is eliminated almost entirely by the kidneys (most likely the elimination is via both filtration and tubular secretion). A large variability in acamprosate

pharmacokinetic parameters was observed throughout the information presented in the submission.

Systemic evaluation of the potential for acamprosate to induce or inhibit other drugs was undertaken in vitro. Acamprosate did not induce CYP1A2 and 3A4 in human hepatocytes (10 and 100 µM). Acamprosate did not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 in human microsomes (10 and 100 µM).

After a short intravenous administration the acamprosate total clearance ranged from 10 to 20 L/h with a mean value of 13.8 L/h. The terminal half-life ranged from 3 to 13.5 hours with a mean value of 5.7 hours. The mean renal clearance value did not differ from that of the total clearance indicating that acamprosate is eliminated via the kidneys. Acamprosate $AUC_{0-\infty}$ values after 333 mg and 666 mg administrations were approximately 24,876 and 38,819 ng.h/mL, respectively.

The absolute bioavailability of acamprosate enteric-coated tablets was estimated to be 11% after 666 mg acamprosate oral administration. The mean terminal half-life was approximately 33 hours.

With respect to dose linearity, the data obtained with the increasing oral solutions, concentration-related pharmacokinetic parameters increase in a linear manner up to 1600 mg/day (800 mg twice daily).

High fat breakfast appears to decrease the absorption of a single dose of acamprosate (approximately 42% and 23% decrease for Cmax and AUC, respectively). In clinical trials the patients were advised to take acamprosate with food.

Acamprosate and disulfiram drug interaction study indicated that there is no pharmacokinetic effect of disulfiram on acamprosate disposition. However, there is no data on the affect of acamprosate on disulfiram. This information may be needed since there is a possibility of concomitant usage of disulfiram and acamprosate.

No drug interactions were observed between (a) acamprosate and diazepam, and (b) acamprosate and imipramine.

There is no effect of acamprosate on the pharmacokinetics of naltrexone, but naltrexone appears to increase the absorption of acamprosate (Cmax was increased by 30%).

Sufficient information to permit assessment of the adequacy of in vitro release method was not provided in the submission and was requested from the Applicant.

Population warranting dosage adjustment

Kidney insufficiency significantly affects acamprosate kinetics, and it appears that there is a good correlation between decrease in creatinine clearance and decrease in acamprosate clearance. Dosage adjustments in renal insufficiency groups (moderate and severe) are recommended. (See attachment 6.3)

The effect of age on the pharmacokinetics of acamprosate was not systematically evaluated. Since renal function diminishes in elderly and acamprosate is excreted unchanged in urine, kidney function (creatinine clearance) should be monitored in this population. Dosage adjustment may be needed accordingly.

Population warranting no dosage adjustment

There is no apparent influence of gender on acamprosate kinetics and therefore no dosage adjustment is warranted based on gender.

There is no influence of mild and moderate hepatic insufficiency on acamprosate kinetics. Although severe hepatic insufficiency was not studied, because acamprosate is not metabolized and mild and moderate hepatic insufficiency did not show any changes, no dosage adjustment is warranted in hepatic insufficient subjects.

Pharmacokinetics of acamprosate are similar in alcohol withdrawn subjects and normal subjects and there is no influence of ethanol on the acamprosate disposition. Likewise, there is no effect of acamprosate on ethanol kinetics.

Pediatric population

Pharmacokinetic or clinical information is not available in pediatric population. The Applicant has requested a deferral to study acamprosate in pediatric population.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-431 (acamprosate enteric-coated tablet) submitted on December 21, 2001 and finds the information contained in the NDA acceptable.

The recommendation and Phase IV commitment comments should be communicated to the Applicant.

1.2 Phase IV Commitments

a) Since acamprosate concentration can accumulate significantly in patients with severe renal impairment when a dosage regimen of 666 mg three times daily is used, provide pharmacokinetic data on a appropriately adjusted dosage regimen that would result in plasma levels comparable to those seen in patients with normal renal function.

b) Since renal function is diminished in the elderly population resulting in significant accumulation of acamprosate, provide comparative pharmacokinetic data in this subgroup in relation to young adults. If warranted, based on the results of this data, propose an appropriately adjusted dosage regimen.

c) Provide pharmacokinetic data on the effect of disulfiram on the pharmacokinetics of acamprosate.

d) With respect to acamprosate enteric-coated tablet dissolution specification the following information request has been communicated to the Applicant and is reiterated below:

   1) Justification of using Method B over Method A;
   2) Dissolution data from 333 mg enteric-coated "current" formulation tablet lot(s) used in pharmacokinetic studies using the proposed method, Method B (e.g., Lot # 1862 from BE study, etc.);
   3) Justification of using [ ] speed; Are there any data from other speeds, [ ]

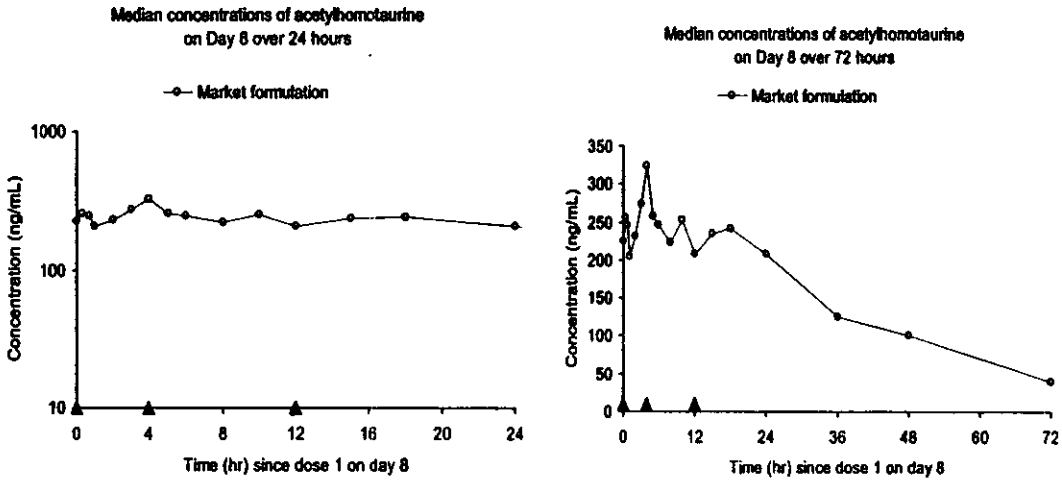
4) Justification for using pH 6.8; Are there any data at other pH values, [ ]
5) Justification of proposing [ ] release [ ] acid solution when [ ] is actually measured;
6) Justification of proposing 120 minutes as a single time point for the buffer solution; Are there any data at time-points earlier than 120 minutes, e.g., 30, 60, etc.?

2 Table of Contents

3 Summary of CPB Findings

Pharmacokinetic properties of acamprosate (acetylhomotaurine) are as follows:

1. After a short intravenous administration the acamprosate total clearance ranged from 10 to 20 L/h with a mean value of 13.8 L/h. The terminal half-life ranged from 3 to 13.5 hours with a mean value of 5.7 hours. The mean renal clearance value did not differ from that of the total clearance indicating that acamprosate is eliminated via the kidneys. Acamprosate AUC_{0-} values after 333 mg and 666 mg administrations were approximately 24,876 and 38,819 ng.h/mL, respectively.
2. A large variability in acamprosate pharmacokinetic parameters was observed throughout the data base.
3. After single dose administration of two 333 mg tablets, peak concentrations are reached 4.5 hours after dosing with the current formulation.
4. After oral administration of two 333 mg acamprosate tablets 3 times daily for 8 days, the geometric mean C_{max} was 353 ng/mL and the area under the curve over 24 hours was 5904 ng.h/mL.
5. After administration of a single dose of two 333 mg tablets, food decreased C_{max} and AUC by 42 and 23%, respectively.
6. The pharmacokinetic profile of acamprosate, administered to healthy subjects at the dose of 666 mg t.i.d., is represented below:



Pharmacokinetic profile of multiple doses of acamprosate, using linear scale (left) and semi-log scale (right). The triangles indicate the dosing times. Median concentrations are plotted.

8. Upon multiple dosing with acamprosate tablets, 666 mg t.i.d. for 8 days, steady-state is reached after 5 days of administration.
9. After oral acamprosate administration acamprosate is not metabolized. A large proportion is eliminated unchanged in the feces, representing unabsorbed drug. The majority of absorbed drug is eliminated unchanged in the urine (11% of the dose).
10. Plasma protein binding of acamprosate is negligible.
11. The pharmacokinetics of acamprosate are not influenced by gender.
12. The renal clearance of acamprosate ranged from approximately 10 to 20 L/h, indicating both filtration and tubular secretion processes.
13. In subjects with varying degrees of renal impairment, clearance of acamprosate decreases proportionally to creatinine clearance.
14. In patients with mild and severe hepatic impairment (either on the basis of chronic alcoholism or other etiologies), there was no difference in pharmacokinetics of acamprosate compared to healthy subjects.

Dug interaction findings

1. Concomitant acamprosate administration had no effect on the pharmacokinetics of ethanol, diazepam or its metabolite nordiazepam, imipramine or its metabolite desipramine, or naltrexone and its metabolite 6-β-naltrexol.
2. The pharmacokinetics of acamprosate was not influenced by the concomitant administration of alcohol.
3. The pharmacokinetics of acamprosate was not influenced by the concomitant administration of disulfiram or diazepam. No information is available on acamprosate affect on disulfiram.
4. There was increase in Cmax and AUC of acamprosate when naltrexone was concomitantly administered.
5. Acamprosate (10 and 100 μM) did not induce CYP1A2 and 3A4 in human hepatocytes. Acamprosate (10 and 100 μM) did not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 in human microsomes.

Bioavailability/bioequivalence results

1. The absolute bioavailability of acamprosate is approximately 11%.
2. After single dose, bioequivalence was established for $AUC_{0-\infty}$, but not for C_{max} after administration of 666 mg tablets of the initial formulation (reference) and the currently marketed formulation (test). A period effect was observed in this study.

3. After administration of 666 mg t.i.d. of the same formulations to steady-state, the formulations were bioequivalent with respect to $AUC_{0-\tau}$, AUC_{0-last} and $AUC_{0-\infty}$ and C_{max}.

Safety Findings from Clinical Pharmacology studies

1. The Applicant stated that acamprosate was well tolerated in healthy subjects after single or multiple doses up to the highest dose levels tested (2664 mg as a single dose or up to 5328 mg total daily dose over 14 days).
2. In healthy subjects, the most frequently reported adverse events were gastrointestinal symptoms of nausea, vomiting, abdominal or epigastric pain, and diarrhea. These were mild to moderate in severity and resolved spontaneously.

4 QBR

4.1 General Attributes

What are some significant drug development milestones?

The Applicant reported the following number of subjects involved in the acamprosate overall clinical pharmacology drug development program: To date (November 2001), the overall clinical pharmacology program of acamprosate consists of 26 studies and 4 supplemental analyses, which have involved 388 subjects (349 healthy volunteer subjects and 39 patients). Six subjects only received placebo. Of these 26 studies, 22 have been conducted in healthy volunteers and 4 in various patient groups, including 9 patients with alcohol dependence, 12 patients with renal impairment, and 18 patients with hepatic impairment. Information on the human pharmacokinetics and bioavailability of acamprosate contained in this NDA is derived principally from 3 sources:

1. Early studies conducted by Laboratories Meram (France), the original developers of acamprosate in France, consisting of the following: Meram: Oct. 27, 1986 (Boismare), entitled: Open study report on the tolerance of calcium acetyl homotaurinate in 10 healthy volunteers; Meram: Feb. 6, 1991 (Jaillon), entitled: Clinical tolerance study of intravenous calcium acetylhomotaurinate (AOTA) in healthy volunteers.
2. Subsequent studies conducted by Lipha S.A. (Lyon, France), who licensed acamprosate from Laboratories Meram and comprehensively continued the preclinical and clinical development of the product worldwide;
3. An additional study, conducted by Lipha Pharmaceuticals, Inc. (New York, NY), as part of the development of acamprosate tablets under IND #51,809 [ACAMP/US/97.1 (Dixon), entitled: A Phase I, pharmacodynamic and pharmacokinetic drug interaction study of acamprosate and naltrexone in normal healthy adult volunteers.].

In addition to the tablet formulations of acamprosate, an oral solution of acamprosate, a lyophilisate for intravenous infusion, and a capsule presentation of acamprosate were also used during the development process. Acamprosate pharmacokinetic development program have included pivotal studies that assessed:

1. Dose proportionality of various dosage forms of acamprosate;
2. Absorption, distribution, metabolism, and elimination;
3. Comparative pharmacokinetics of single and multiple oral doses of oral solutions and tablets; bioequivalence studies of key tablet formulations including recent reanalyzes and integrated analyses;
4. Influence of food;
5. Gender on pharmacokinetics;
6. Comparison of kinetics in the target population of chronic alcoholic patients;

7. Studies in renal-impaired and hepatic-impaired; and,
8. Interactions with various other relevant substances or products (including ethanol, disulfiram, diazepam, imipramine, and naltrexone.

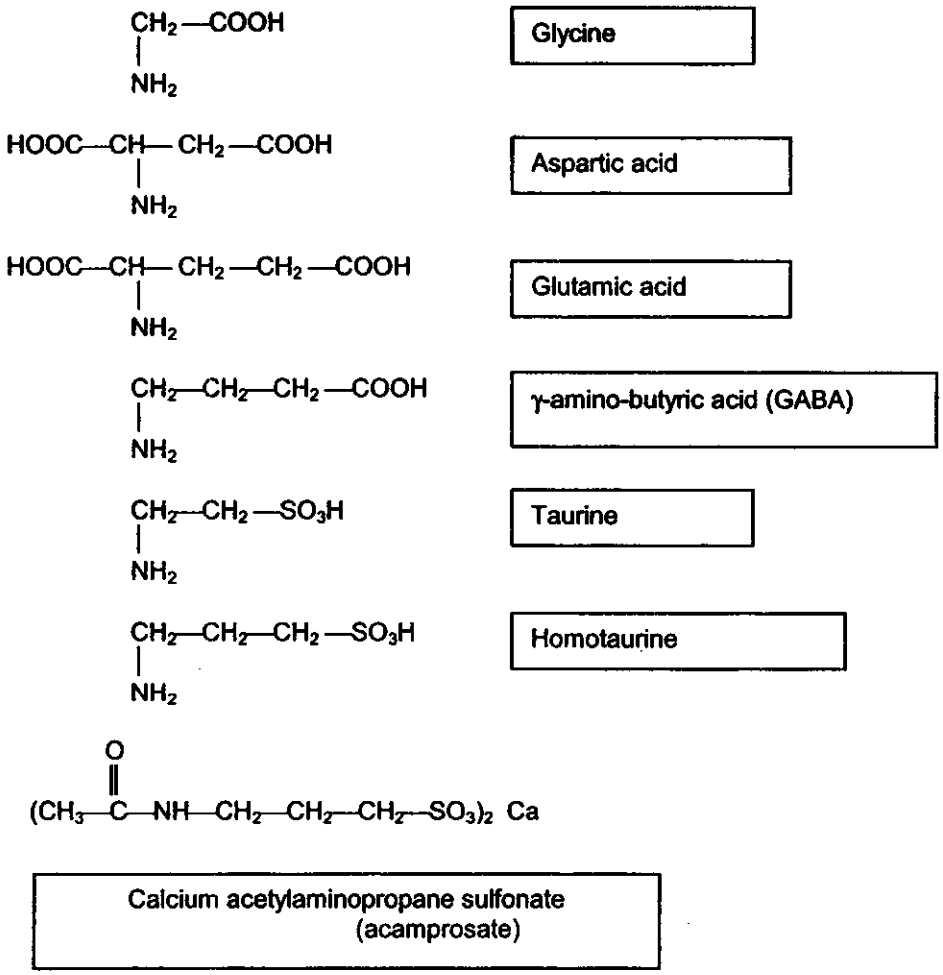
What is acamprosate's mechanism of action?

Acamprosate, calcium acetylhomotaurinate (calcium 3-acetylaminopropane sulfonate), a new chemical entity, is a synthetic homotaurine (see figure below) derivative developed for use in subjects with alcohol dependence. At present, the state of alcohol dependence, from a physiologic perspective, is believed to result in disturbance of the fundamental balance in the brain between the inhibitory transmitter GABA and the excitatory transmitter glutamate.

The Applicant provided the following information regarding acamprosate and related structures of acamprosate:

"...In the central nervous system, certain amino acids, classified as either excitatory or inhibitory, are putative neurotransmitters or neuromodulators. Homotaurine (3-amino-propanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, both of which have structural similarities to the neurotransmitter, γ-amino butyric acid (GABA). Taurine and GABA are considered to be inhibitory, centrally active amino acids.

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 that is not naturally occurring, cannot enter the central nervous system, because of the impermeability of the blood-brain barrier to zwitterions. Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine. In addition, acamprosate has structural similarities to glycine and to the excitatory neurotransmitters, aspartate and glutamate (a precursor of GABA). 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.



Acamprosate structure, relative to other key amino acids

The discovery of acamprosate's action on voluntary alcohol intake in animals and its pharmaceutical development, initiated by Laboratoires Meram and continued thereafter by Lipha s.a., has paralleled research into the neurobiological and neurochemical mechanisms of alcohol dependence.

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.

In summary, acamprosate appears to restore the fundamental balance in the brain between the inhibitory and excitatory transmitters, which is thought to be disturbed in chronic alcoholism. Through normalization of function of glutamate receptors of the NMDA receptor subtype, acamprosate may both reduce cravings, which occur during abstinence from alcohol, and reduce the reinstatement of dependence if relapse occurs. "

What is acamprosate tablet composition?

Acamprosate (calcium acetylhomotaurinate) was originally identified by Laboratories Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. It was authorized for marketing in France in 1987 (as Aotal®) and has been commercially available since 1989 in the 333 mg strength. Currently, acamprosate is available in 38 additional countries around the world, primarily under the name Campral®.

The initial Meram formulation of acamprosate 333 mg enteric-coated tablets is labeled as the "initial formula." This tablet formulation was slightly modified by Lipha s.a. to meet current international industrial requirements and is currently marketed worldwide. This formula is labeled as the "current formula" and also referred to in the preceding clinical pharmacokinetic sections as the "currently marketed formulation" or "test formulation."

The Applicant stated that these tablets have similar dissolution and stability characteristics to the reference or initial formulation. In addition, these two formulations were linked through single and multiple dose bioequivalence studies.

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. Additionally this 500 mg tablet was used in the pivotal US96.1 safety and efficacy trial. At present time the Applicant is not seeking the approval of this strength. The 500 mg strength and 333 mg strength were studied in a multiple dose study that compared two 333 mg tablet given three times daily versus two 500 mg tablets given two times daily.

Composition of Acamprosate Tablets: Initial formula and Current formula

Ingredient	Initial formula		Current formula		
	333 mg tablets Quantity/tablet (mg)	Quantity per tablet (%)	333 mg tablets (marketed tablets) Quantity/tablet (mg)	500 mg tablets* Quantity/tablet (mg)	Quantity per tablet (%)
Tablet cores					
Calcium-acamprosate	333.0		333.0	500.0	
Crospovidone or equivalent)					
Microcrystalline cellulose equivalent) equivalent)					
Magnesium silicate equivalent)					
Sodium starch glycolate equivalent)					
Colloidal silica equivalent)					
Magnesium stearate					
Total cores					
Tablet coating					
Anionic copolymer of methacrylic acid and acrylic acid ethyl ester (in the form of an aqueous dispersion as Eudragit L30D or equivalent)					
Talc					
Propylene glycol					
Total coating					
Total coated tablet	525.0	-	531.6	783.0	-

* 500 mg tablets have the same composition as 333 mg: the tablet weight was adapted from the 333 mg tablets in order to obtain 500 mg of calcium-acamprosate as dosage strength, while keeping the same ratio in excipients. Consequently, the designation of "current formula" is also valid for 500 mg tablets. This formulation was used in the pivotal US96.1 safety and efficacy trial.

The Applicant stated that the formulation was modified in order to scale up and optimize the industrial production level and also to enable tablet manufacturing to be done at the Lipha s.a. site, Centre de Production Lacassagne, Lyon, France. See below for 4 minor production modifications:

a.

b.

c.

d.

4.2 General Clinical Pharmacology

What is the basic pharmacokinetic characteristics of acamprosate?

A summary of the main pharmacokinetic parameters following single intravenous administration to twelve healthy subjects infused over 15 minutes in fasting state is presented below in the following Table.

Mean (%CV), Minimum, And Maximum Values Of Selected Pharmacokinetic Parameters After Intravenous Administration Of 333 Mg Acamprosate (150 mg/10 mL)

Pharmacokinetic Parameter[a]	Mean (±S.D.)	C.V. (%)	Min.-Max
C_{max} (ng/mL^{-1})	27,869 (6,916)	25	
T_{max} (h)	0.25		
AUC_{0-t} (ng.h/mL)	24,832 (4,411)	18	
$AUC_{0-\infty}$ (ng.h/mL)	24,876 (4,427)	18	
$t_{1/2}$ (h)	5.7 (2.8)	49	
Ae (mg)	347.5 (18.3)	5	
Cl_T (L/h)	13.8 (2.7)	20	
Cl_R (L/h)	14.4 (2.9)	20	
Vd (L)	109.5 (41.7)	38	

Values based on data from 12 subjects

The Applicant stated that there were difficulties with urine collection, thus, difficulty in achieving precise measurements of urine volume of collected fractions and coefficient of variation of the analytical method may have accounted for recovery of more than 100% of the administered dose in some subjects. However, the acamprosate collected in urine indicated that renal excretion was the sole route of elimination of acamprosate, following intravenous infusion.

What is the absolute bioavailability of acamprosate tablet?

Following a single oral dose of two 333 mg acamprosate tablets, the absolute bioavailability was estimated to be 0.11 (±0.01). The data indicated that plasma terminal half-lives were 32.7±4.3 hours and 3.2±0.2 hours with the oral and intravenous administrations, respectively.

Acamprosate Pharmacokinetic Parameters Following a Single Oral Dose of Acamprosate Tablets (2x 333 mg dose; total of 666 mg) and a Single Intravenous Dose of 666 mg in 24 Healthy Subjects

Pharmacokinetic Parameters	Oral Dosing (n = 24)	Intravenous Dosing (15 min. infusion) (n = 24)
Acamprosate Dose	666 mg (tablets)	666 mg (IV infusion)
C_{max} (ng/mL)	206 ± 23	38,819 ± 1,898
T_{max} (h)	5.2 ± 0.6	0.24 ± 0.05
$AUC_{0-\infty}$ (ng•h/mL)	4110 ± 442	39,696 ± 1737
$t_{1/2}\lambda z$ (h)	32.7 ± 4.3	3.2 ± 0.2
MRT (h)	47.7 ± 5.7	1.54 ± 0.03
MAT (h)	46.2 ± 5.7	--
CL/F (mL/min)	2981 ± 253	--
CL (mL/min)	--	263 ± 12
$U_{0\text{-}96\ hrs}$ (% of administered dose)*	5.4 ± 0.6	49 ± 5.4
F	0.11 ± 0.01	--
V_{ss} (L)	--	24 ± 1

*The Applicant stated that urine collection was incomplete. Thus, this value is questionable.

Is there any exposure-response relationship information for acamprosate?

The information submitted by the Applicant did not contain any exposure-response information. However, the Applicant stated that it is difficult to define a exposure-response curve for drugs used in a disease such as alcohol dependence "which lacks clear-cut, universally accepted biological or physiological endpoints which can be accurately monitored." In order to elaborate on this issue the Applicant stated that in the past some of the surrogate or biological markers used in order to assess recent and chronic excessive drinking were elevation of gamma-glutamyl transferase (GGT), carbohydrate deficient transferrin (CDT) levels and elevation of mean corpuscular volume (MCV) of red blood cells, elevated liver enzymes including GGT, respectively; however, these were taken as supportive evidence measurements. Additionally, the clinician's global assessment of the patient's improvement has been used as an endpoint, and, mostly it is a combination of these assessments which allows judgment to be made as to whether or no the patient is continuing to drink and whether or not there has been improvements. The Applicant's approach was to use the endpoint of cumulative abstinence duration (CAD), either in absolute terms or as a percentage of the amount of time on study (corrected CAD). The current submission appears not to contain acamprosate exposure-response information. The majority of studies including the pivotal studies utilized 1998 mg/day dose.

In the current submission the Applicant stated that two studies of the 3 efficacy studies (Pelc II and Paille) have looked at 2 parallel dose groups of acamprosate (1332 mg/day and 1998 mg/day. The duration of studies was 90 days and 360 days for Pelc II and Paille, respectively. The third efficacy study (PRAMA) was conducted at the total daily dose of 1998 mg. The duration of this study was 48 weeks or 336 days. The Applicant reported that results from the studies seem to indicate that there was no strong evidence of 1332 mg/day leading to effectiveness, however, 1998 mg/day dose was effective. It is interesting to note that, according to the medical officer who assessed acamprosate safety in the current submission, France government authority requested the Applicant to study the effectiveness of 1998 mg/day regimen after the initial acamprosate approval in 1989. From a safety perspective, the Applicant reported that there seems to be increase in GI AE events (especially diarrhea) with increase in dose from 1332 to 1998 mg/daily, however, doses were well tolerated. Additionally, a dose ranging study performed in 1988 of multiple doses of acamprosate tablets, given twice daily, suggested an increase in AE at or above a total daily dose of 2664 mg/day. This study was a dose ranging study exploring from 666 to 5328 mg daily in two divided doses for 14 days.

Does acamprosate pharmacokinetics change with multiple dosing?

After single administration of oral acamprosate solution at increasing doses, there was a linear correlation between acamprosate exposure and plasma peak up to 2664 mg. However, after repeated dosing, C_{max} and AUC increase less than proportionally at multiple doses above 800 mg given twice daily:

Pharmacokinetic Parameters Following Multiple Doses of Oral Acamprosate Solution, Administered to Healthy Volunteers: Mean Values and Comparisons

Pharmacokinetic Assessment	Dose Levels*				Linearity Tests	
	Treatment A (300 mg b.i.d.) n = 12	Treatment B (500 mg b.i.d.) n = 12	Treatment C (800 mg b.i.d.) n = 12	Treatment D (1000 mg b.i.d.) n = 12	A, B, C, D	A, B, C
$C_{max(ss)}$ (ng/mL)	378.37	566.48	804.47	751.70	p<0.1	NS
$C_{max(ss)}$ proportional to dose	1.000	0.898	0.797	0.596	p<0.1	NS
$T_{max(ss)}$ (h)	171.15	170.48	171.83	172.35	NS	NS
$T_{max(ss)}$ proportional to dose	1.000	0.996	1.004	1.007	NS	NS
AUC (ng.h/mL)	3254.48	4883.36	7744.85	7736.01	NS	NS
AUC proportional to dose	1.000	0.900	0.892	0.713	NS	NS

* At each dose level, subjects received 2 unit doses per day (b.i.d., q12h).

Is acamprosate pharmacokinetics different in alcoholics?

A multiple dose open-label acamprosate study was conducted in alcohol-dependent subjects following their withdrawal from alcohol (abstinent for at least 5 days). No significant difference existed between the mean (±SD) values of $AUC_{(0\text{-}24h)}$ on Day 7 (9695 ± 5126 ng.h/mL) and on Day 28 (12,363 ± 9995 ng.h/mL), although there was a great deal of variability between subjects.

Dose acamprosate protein bind?

The Applicant conducted an equilibrium dialysis study. Plasma protein binding of acamprosate is negligible.

Is acamprosate metabolism elucidated?

Initially, two radiolabeled studies were conducted [^{35}S-acamprosate (^{35}S-AOTA-Ca), as an aqueous solution in two healthy subjects and ^{14}C-acamprosate (^{14}C-Aota-Ca), as an aqueous solution in four healthy subjects]. Both studies utilized thin-layer chromatography (TLC) and high performance liquid chromatography (HPLC).

The ^{35}S study showed in pooled plasma and urine samples presence of both acamprosate (N-acetylhomotaurine) and homotaurine, which possibly represented metabolic deacetylation of acamprosate. Contrast to ^{35}S study, the ^{14}C study showed only acamprosate from radio-HPLC analysis of pooled urine and fecal samples. No "significant" peak with a retention time similar to homotaurine was observed; however, the radio-chromatogram showed that this peak was detectable and was not quantitated. This reviewer presumes that the Applicant considered the concentration of this peak to be insignificant and did not warrant further investigation. Excretion via the urinary route accounted for a mean of 11.0% of the administered radioactivity. A mean of 88.2% of administered radioactivity was recovered from the feces of the administered radioactivity over 120 hours.

In all subsequent clinical pharmacology studies, a validated GC/MS method was utilized. Both plasma and urine samples analyzed by the GC/MS assay showed only acamprosate and no homotaurine was observed. Thus, regarding findings from the ^{35}S study, it appears that samples prepared (both standard and actual samples) were perhaps contaminated prior to assay. Finally, due to the overwhelming data presented from the GC/MS assay, this reviewer considered that

acamprosate does not undergo metabolism process, although there was a hint of deacetylation process.

What is the main elimination route for acamprosate?

As stated above acamprosate appears to not undergo metabolism process. Excretion of absorbed acamprosate was determined to be via the renal route. The remaining unabsorbed acamprosate was detected in fecal samples. From the radioactivity studies the major portion of absorbed acamprosate was eliminated in urine during the first 24 hours post dosing.

Does acamprosate show dose proportionality in the proposed mass dose range?

The Applicant is proposing one dose only (two 333 mg tablet three times daily). There were no "formal" dose ranging studies conducted with the proposed tablet. However, the Applicant conducted dose ranging studies using acamprosate solutions. This information should provide further insights into acamprosate's disposition characteristics without the formulation affect. The data indicated that the variability of pharmacokinetic parameters were large. Overall, single dose administration showed dose linearity up to 2664 mg. However, non-linearity was seen after multiple dosing.

A single dose, oral solution study was conducted in six healthy male subjects where acamprosate was administered at 7 day intervals, following an overnight fast, at the following dose levels: 333 mg, 666 mg, 1332 mg, and 2664 mg. The investigator concluded that there appeared to be a good linear correlation between C_{max} and oral dose (R^2 = 0.9401) and between AUC and oral dose (R^2 = 0.9906, excluding the 333 mg dose level). At acamprosate doses of 333 mg, 666 mg, 1332 mg, and 2664 mg, the percentage of administered dose that was excreted unchanged in the urine was 4.9-6.8% (333 mg), 4.1-8.2% (666 mg), 5.3-7.8% (1332 mg), and 4.1-9.9% (2664 mg), respectively.

Mean (SD) Pharmacokinetic Variables Following Single Dose Oral Solutions of Acamprosate

Acamprosate Dose Level in mg (Number of Subjects)	C_{max} (ng/mL)	T_{max} (h)	AUC_∞ (ng•h /mL)	$t_{1/2}$ (h)	CL_R (L/h)
333 (n = 6)	325.9 (143.3)	1.42 (0.2)	1155.4 (657.8)	2.0 (0.7)	23.8 (16.6)
666 (n = 6)	782.8 (257.4)	1.5 (0.5)	5442.5 (1888.0)	13.0 (3.2)	7.7 (2.3)
1332 (n = 6)	914.0 (316.0)	1.4 (0.5)	7196.9 (2316.8)	12.5 (3.7)	12.9 (3.5)
2664 (n = 6)	1549.5 (744.3)	1.2 (0.5)	12624.2 (5265.0)	14.5 (3.4)	16.9 (7.6)

A randomized (within group), double-blind, placebo-controlled, 4-dose level, sequential, multiple dose, rising dose pharmacokinetic and tolerability study was conducted in sixty-two male healthy subjects. Volunteers were fasted over night for 10 hours blood samples and meals were served approximately 30 minutes after dosing. The 4 treatment groups were as follows:

Group I (Treatment A):	300 mg/10 mL b.i.d. for 8 days (600 mg/day);
Group II (Treatment B):	500 mg/10 mL b.i.d. for 8 days (1000 mg/day);
Group III (Treatment C):	800 mg/10 mL b.i.d. for 8 days (1600 mg/day);
Group IV (Treatment D):	1000 mg/10 mL b.i.d. for 8 days (2000 mg/day).

According to the data, steady state appeared to be reached at Day 6 for Treatments A, B, and C. For Treatment D (1000 mg b.i.d.), there was a significant decrease in mean trough plasma concentration from Day 6 to 7 and then a non-significant increase from Day 7 to Day 8. There was no statistically significant difference between treatment groups for renal clearance. No significant difference was detected between treatment groups for this parameter or for T_{max}.

Terminal Half-Life and Renal Clearance at Steady State, Following Multiple Doses of Oral Acamprosate Solution, Administered to Healthy Volunteers: Mean (SEM) Values

	Treatment Groups			
	Treatment A (300 mg b.i.d.) n = 12	Treatment B (500 mg b.i.d.) n = 12	Treatment C (800 mg b.i.d.) n = 12	Treatment D (1000 mg b.i.d.) n = 12
CL_R (mL/min)	229.51 (23.50)	269.76 (39.06)	267.55 (23.87)	205.39 (14.80)

* For this parameter, n = 9.
** For this parameter, n = 10.

Pharmacokinetic Parameters Following Multiple Doses of Oral Acamprosate Solution, Administered to Healthy Volunteers: Mean Values and Comparisons

Pharmacokinetic Assessment	Dose Levels*				Linearity Tests	
	Treatment A (300 mg b.i.d.) n = 12	Treatment B (500 mg b.i.d.) n = 12	Treatment C (800 mg b.i.d.) n = 12	Treatment D (1000 mg b.i.d.) n = 12	A, B, C, D	A, B, C
$C_{max(ss)}$ (ng/mL)	378.37	566.48	804.47	751.70	p<0.1	NS
$C_{max(ss)}$ proportional to dose	1.000	0.898	0.797	0.596	p<0.1	NS
$T_{max(ss)}$ (h)	171.15	170.48	171.83	172.35	NS	NS
$T_{max(ss)}$ proportional to dose	1.000	0.996	1.004	1.007	NS	NS
AUC (ng.h/mL)	3254.48	4883.36	7744.85	7736.01	NS	NS
AUC proportional to dose	1.000	0.900	0.892	0.713	NS	NS

* At each dose level, subjects received 2 unit doses per day (b.i.d., q12h).

The $C_{max(ss)}$ and $AUC_{0-24(ss)}$ increased in a linear manner with increasing dose for the first 3 groups, but at the dose level of 800 mg two times daily, there appeared to reach a plateau, and linearity was not confirmed.

4.3 Intrinsic Factors

Is there any gender differences in acamprosate pharmacokinetics?

There was no significant difference between men and women for any acamprosate pharmacokinetic parameter after single oral administration of acamprosate. Again this reviewer observed a rather large variability in acamprosate pharmacokinetic parameters.

Mean (SD) Values for Pharmacokinetic Parameters for Female and Male Subjects Following A Single Oral Dose of Acamprosate Tablets (666 mg)

Pharmacokinetic Parameter	Mean (SD) for Females (n = 12)	Mean (SD) for Males (n = 12)	p-value
C_{max} (ng/mL)	212 (83)	188 (81)	0.485
T_{max} (h)	4.25 (1.16)	4.96 (1.89)	0.280
$AUC_{0-\infty}$ (ng.h/mL)	3866 (2011)	3242 (2885)	0.545
AUCt (ng.h/mL)	3571 (1941)	2854 (2679)	0.461
$t_{1/2}$ (h)	28.4 (15.1)	27.5 (18.8)	0.903

Is there any age differences in acamprosate pharmacokinetics?

The effect of age on the pharmacokinetics of acamprosate was not systematically evaluated. Since renal function diminishes in elderly and acamprosate is excreted unchanged in urine, kidney function (creatinine clearance) should be monitored in this population. Dosage adjustment may be needed accordingly.

Does the liver function affect acamprosate pharmacokinetics?

An open-label, in-patient study of the pharmacokinetics of acamprosate, following multiple oral doses was conducted in subjects with varying degrees of hepatic impairment (mild and moderate hepatic insufficiency, Grades A and B, according to the Child-Pugh classification) compared to healthy volunteers.

The results indicated that there was no evidence that impaired liver function affected the pharmacokinetics of acamprosate. This reviewer concurs with the Applicant's conclusion, as acamprosate appears to not undergo any metabolism and eliminated as a parent drug. There were no statistically significant differences in the mean values for C_{min}, C_{max}, T_{max}, AUC, or Ae between the 2 groups of hepatic-impaired patients and the volunteer control group. Again, inter-individual variability for acamprosate appears to be large.

Mean (SD) Values for Pharmacokinetic Parameters after Multiple Doses of Acamprosate: Healthy Volunteers Compared to Patients with Liver Impairment

Pharmacokinetic Parameter	Mean Values (± S.D.) for Subject Group			Statistical test
	Healthy volunteers (n = 6)	Mild liver impairment (n = 6)	Moderate liver impairment (n = 6)	
C_{min} (ng/mL)				
Day 2, H0	233±116	280±109	269±181	
Day 6, H0	449±280	397±125	472±278	NS
Day 7	265±187	146±105	287±324	
Day 8	158±95	123±109	271±363	
C_{max} (ng/mL)				
Day 1	360±66	352±134	388±120	
Day 7	644±386	588±241	683±508	NS
Day 8	534±195	556±317	601±601	
T_{max} (h)				
Day 1	15.3±6.4	16.8±9.3	13.7±8.7	
Day 7	7.3±4.4	13.7±11.6	9.3±10.0	NS
Day 8	3.5±0.5	3.8±2.1	6.2±5.1	
T ½ (h)	13.0±2.9	12.9±7.1	20.0±19.8	NS
$AUC_{0\text{-}24h}$ (ng.h/mL)				
Day 1	3973±836	4046±2067	3596±836	NS
Day 7	9728±5491	7002±3822	10,957±10,398	
Ae (mg/24 h)				
Day 6	98.1±39.0	91.0±28.4	110.6±73.5	NS
Day 7	91.2±47.8	87.5±43.1	119.8±62.6	

Does the kidney function affect acamprosate pharmacokinetics?

An open-label study of acamprosate pharmacokinetics in healthy subjects and subjects with stable moderate to severe renal impairments (creatinine clearance in the range of 30-60 and 5-29 mL/min/1.73 m^2, respectively) was conducted. Each participant received a single oral dose of 666 mg acamprosate (two 333 mg tablets) along with 150 mL of water, following an overnight fast. Breakfast and usual medication (excluding antacids, H2-receptor antagonists, or resin) were permitted 2 hours after dosing.

Total apparent plasma clearance (Cl/F) and renal clearance (Cl_R) of acamprosate showed significant differences between the 3 groups, with reduction in both total clearance and renal clearance in subjects with renal impairment. The greatest reductions were seen in the group with severe renal impairment. C_{max} and T_{max} were also significantly different between groups. Additionally, the data indicated that there was a linear correlation between individual values for creatinine clearance and the corresponding values for acamprosate: total apparent plasma

clearance, CL/F (R = 0.8235; p<0.001); acamprosate renal clearance, CL_R (R = 0.8932; p<0.001), plasma half-life, $t_{1/2}$ (R = 0.4666; p<0.05) and mean residence time, MRT (R = 0.5186; p<0.05).

This reviewer suggests that a dosage adjustment should be warranted in renally impaired patients. There is no doubt that chronic administration of acamprosate in these population will lead to accumulation of acamprosate.

Mean (SEM) Pharmacokinetic Parameters

	Group 1 Healthy Subjects	Group 2 Cr.Cl. 30-60 ml/min	Group 3 Cr.Cl. 5-29 ml/min	Statistics
C_{max} (ng/mL)	198±38	398±78	813±109	p<0.001**
T_{max} (h)	5.83±1.33	4.33±0.76	23.33±7.67	p<0.05†
$t_{1/2}$ (h)	18.21±3.21	33.35±6.58	46.62±12.85	p<0.05†
MRT(h)	28.14±3.45	55.08±11.67	70.58±16.31	NS†
CL/F (L/h)	184.00±25.84	66.50±18.19	15.83±4.51	p<0.01†
CL_R (L/h)	10.05±1.22	3.29±0.85	1.10±0.21	p<0.01†
U %	5.57±0.79	4.26±0.63	6.19±0.76	NS**

* Mann and Whitney U test
** One-way ANOVA
† Kruskal-Wallis test

A further analysis will be needed in this population for a dosage adjustment (forthcoming: Dr. Sam Haidar's analyses).

4.4 Extrinsic Factors

Does food affect the bioavailability of acamprosate tablet?

The bioavailability of single dose acamprosate was significantly decreased with food (Cmax and AUC decreased approximately 42 % and 23 %, respectively) when acamprosate was administered after single oral dose under fasting condition. Decreases in Cmax and AUC are may not be clinically significant.

Effects of Food on Pharmacokinetic Parameters of Acamprosate

Dosing Condition of 666 mg Acamprosate Tablets (Number of Subjects)	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	$AUC_{(t)}$ (ng/mL·h)	$U_{(96)}$ (mg)	U (% of dose)
Fasting (n = 12)		9.58 (3.55)	2.37 (0.20)	2555 (257)	34.83 (2.29)	5.8 (0.4)
Fed state (n = 12)		6.92 (1.71)	2.68 (0.22)	1970 (221)	29.96 (2.70)	5.0 (0.4)
p-value	<0.05**	NS**	NS**	<0.05*	NS* (27%)	

* ANOVA (Westlake)
** Wilcoxon matched paired rank test

Does acamprosate show any drug interactions?

The Applicant explored the following in vitro and in vivo drug interaction studies:

In vitro studies

Acamprosate (10 and 100 μM) did not induce CYP1A2 and 3A4 in human hepatocytes.
Acamprosate (10 and 100 μM) did not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 in human microsomes.

CYP	Medium	Acamprosate ability to :	Reference Inducers and Inhibitors[2]	Control and Metabolite activities tested with:	Acamprosate Conc. used 10 μM	100 μM
1A2	Hepatocytes[1]	[redacted]	Inducer 3-methylcholanthrene (5 μM)		No	No
	Microsomes[1]	Inhibit	Inhibitor α-naphtoflavone (10 μM)[3]	Phenacetin deethylase	No	No
2C9	Microsomes	Inhibit	Inhibitor Sulfaphenazole (5 μM)[4]	Tolbutamide hydroxylase	No	No
2C19	Microsomes	No inhibitor tested*	(S)-mephenytoin (20 μM)[5]	(S)-mephenytoin hydroxylase	No	No
2D6	Microsomes	Inhibit	Inhibitor Quinidine (2 μM)[6]	Dextromethorphan demethylase	No	No
2E1	Microsomes	No inhibitor tested*	Chlorzoxazone (200 μM)	Chlorzoxazone hydroxylase	No	No
3A4	Hepatocytes	[redacted]	Inducer Rifampicin (50 μM)		No	No
	Microsomes	Inhibit	Inhibitor Ketoconazole (1 μM)[7]	Nifedipine oxidase	No	No

*The Applicant state that the literature does not mention specific inhibitors for 2C19 and 2E1.

1: Human microsomes and hepatocyte cultures
2: Medium incubated for 20 - 30 minutes in the presence of acamprosate or the reference.
3: Also in the presence of the *substrate phenacetin at 40 μM* and of the cofactor at 2 mM.
4: Also in the presence of the *substrate tolbutamide at 200 μM* and of the cofactor at 1 mM.
5: Also in the presence of the cofactor at 2 mM.
6: Also in the presence of the *substrate dextromethorphan at 20 μM* and of the cofactor at 2 mM.
7: Also in the presnece of the *substrate nifedipine at 20 μM* and of the cofactor at 2 mM.

In vivo studies

Acamprosate and alcohol

The pharmacokinetic parameters for ethanol (C_{max}, T_{max} and AUC_{0-t}) in healthy volunteers following a single oral dose of approximately 32 g ethanol, consumed over 30 seconds, did not differ significantly in the presence or absence of acamprosate pre-treatment for several days, at a total daily dose of 1998 mg.

Acamprosate tablets, given as a single oral dose of 1332 mg, were administered to healthy subjects both with and without concomitant alcohol administration. The rate and extent of absorption of acamprosate with alcohol was not statistically significantly different from the rate and extent of absorption without alcohol.

Disulfiram on acamprosate

This study was an open-label, randomized, 2 period cross-over study of the pharmacokinetics of acamprosate and disulfiram when given separately and concomitantly.

Acamprosate pharmacokinetic parameters were not affected by disulfiram co-administration. However, due to the disulfiram assay problem the acamprosate affect on disulfiram was not assessed.

Pharmacokinetic Parameters During Multiple Dosing of Acamprosate Alone or with Multiple Doses of Disulfiram

Pharmacokinetic Parameter*	Acamprosate Alone (Day 7)		Acamprosate + Disulfiram (Day 14)	
	Mean	SD	Mean	SD
AUC_{0-4h}**	1059.58	511.76	1157.22	660.45
AUC_{4-12h}**	1955.08	768.51	2314.21	1078.45
AUC_{12-24h}**	2606.68	1166.33	2823.11	1688.20
AUC_{0-24h}**	5621.34	2343.16	6294.54	3113.32
C_{ss} (ng/mL)	234.22	97.63	262.27	129.72
C_{max} (ng/mL)	369.72	145.35	418.54	215.03
T_{max} (h)	5.45 (4.0)†	6.22	6.05 (5.0)†	5.74

* Values are based on data from all 20 subjects.
** Values for AUC are given as $ng \cdot mL^{-1} \cdot h$.

Acamprosate on diazepam

This study was an open-label, randomized, 2 period cross-over study of the pharmacokinetics of acamprosate and diazepam when given alone and in combination. Since diazepam may be used as a medication during alcohol withdrawal, it was of interest to administer it as monotherapy prior to concomitant therapy with acamprosate. This study showed that there was no evidence of pharmacokinetic interaction of either diazepam and its metabolite (nordiazepam) or acamprosate when given in combination on multiple oral dosing.

Mean Values of Pharmacokinetic Values of Diazepam and Nordiazepam, When Given as Monotherapy and Co-administered with Acamprosate

	Day 7 (Diazepam Alone) (n = 16)		Day 14 (Diazepam and Acamprosate) (n = 16)		Day 7/Day 14 (% of Day 14) (n = 16)	
Plasma Analyte	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)
Diazepam	6469	269.5	7469	311.2	86.6%	86.6%
Nordiazepam	6334	263.9	8956	373.4	70.7%	70.7%

Acamprosate and imipramine

Decourt II study was an open-label, randomized, 2 period, cross-over study of the pharmacokinetics of imipramine when given alone and when given in combination with acamprosate. It was concluded that there was no significant difference in the pharmacokinetic patterns of either imipramine or its metabolite desipramine after single oral dosing of imipramine alone or when given on Day 7 of multiple oral dosing with acamprosate (666 mg tid).

Pharmacokinetic Parameters of Imipramine after Administration of Imipramine with Acamprosate (Treatment A) or Alone (Treatment B)

Pharmacokinetic Parameter	Mean (SD) and [Minimum, Maximum] Values by Treatment Group		Statistical Analysis
	Treatment A (acamprosate and imipramine) (n = 16)	Treatment B (imipramine alone) (n = 16)	
C_{max} (ng/mL)	25.26 (8.30)	25.54 (9.87)	NS* (0.89-1.14)
T_{max} (h)	2.3 (1.0)	2.4 (0.7)	NS**
$t_{1/2}z$ (h)	12.6 (1.9)	13.8 (3.2)	P<0.05* (0.84-0.98)
AUC (ng.h/mL)	271.2 (96.0)	299.3 (120.2)	NS* (0.83-1.04)

* = ANOVA (90% confidence interval around the ratio Treatment B/Treatment A)
** = Wilcoxon test

Pharmacokinetic Parameters of Desipramine after Administration of Imipramine with Acamprosate (Treatment A) or Alone (Treatment B)

Pharmacokinetic Parameter	Mean (SD) and [Minimum, Maximum] Values by Treatment Group		Statistical Analysis
	Treatment A (acamprosate and imipramine) (n = 16)	Treatment B (imipramine alone) (n = 16)	
C_{max} (ng/mL)	8.02 (2.32)	8.04 (2.75)	NS*
T_{max} (h)	3.6 (2.0)	7.1 (14.1)	NS**
$t_{1/2}z$ (h)	18.83 (3.41)	21.94 (8.11)	NS**†
AUC (ng.h/mL)	195.4 (74.7)	215.8 (105.9)	NS*†

* = 2-way ANOVA
** = Wilcoxon test
† = 15 subjects

Acamprosate and naltrexone

This study was a double-blind, randomized, 3 period cross-over study of the pharmacokinetics and pharmacodynamics (cognitive function assessments) of acamprosate and naltrexone when multiple doses of these drugs were given separately and in combination.

There was a statistically significant pharmacokinetic interaction when acamprosate was administered twice a day in combination with a once daily administration of naltrexone for 7 days. Coadministration of naltrexone with acamprosate increased the rate and extent of absorption of acamprosate, 33% and 25 % increases in acamprosate C_{max} and AUC_{0-T}, respectively, and the shorter T_{max} values. Naltrexone did not affect the elimination half-life of acamprosate. Acamprosate had no effects on the pharmacokinetic parameters of naltrexone or its major metabolite 6-β-naltrexol.

Mean (SD) and Minimum, Maximum Values for Acamprosate Pharmacokinetic Parameters, Following Multiple Doses of Acamprosate Alone or with Naltrexone

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Acamprosate (Treatment A) (n = 24)		
C_{max} (ng/mL)	517 (183.6)	390 (160.0)	133	(118, 148)** (120, 156)†
AUC_{0-T} (ng.hr/mL)	4658 (1778.2)	3734 (1644.2)	125	(112, 137)** (114, 143)†
$T_{1/2}$ (h)	17.9 (8.81) ††	18.5 (14.9) ‡	119	NA
T_{max} (h)	5.44 (3.08)	6.38 (2.87)	NA	NA

* = Test = Treatment C; Reference = Treatment A. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.
†† = n = 19
‡ = n = 20

Mean (SD) and Minimum, Maximum Values for Naltrexone Pharmacokinetic Parameters, Following Multiple Doses of Naltrexone Alone or with Acamprosate

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Naltrexone (Treatment B) (n = 24)		
C_{max} (ng/mL)	11.0 (4.76)	11.8 (6.55)	93.3	(79.6, 107)** (85.0, 109)†
AUC_{0-T} (ng.hr/mL)	38.0 (16.07)	38.6 (16.53)	98.4	(90.1, 107)** (92.0, 106)†
$T_{1/2}$ (h)	3.58 (1.62)	4.02 (3.49)	89.1	NA
T_{max} (h)	1.19 (0.46)	1.23 (0.33)	NA	NA

* = Test = Treatment C; Reference = Treatment B. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.

Mean (SD) and Minimum, Maximum Values for 6-β-Naltrexol Pharmacokinetic Parameters, Following Multiple Doses of Naltrexone Alone or with Acamprosate

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Naltrexone (Treatment B) (n = 24)		
C_{max} (ng/mL)	91.3 (19.34)	96.1 (21.05)	95.0	(87.2, 103)** (88.1, 103)†
AUC_{0-T} (ng.hr/mL)	779 (128.3)	788 (134.8)	98.8	(95.0, 103)** (95.4, 103)†
$T_{1/2}$ (h)	15.1 (4.18)	14.7 (3.88)	103	NA
T_{max} (h)	1.25 (0.49)	1.21 (0.36)	NA	NA

* = Test = Treatment C; Reference = Treatment B. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.

4.5 General Biopharmaceutics

Are acamprosate clinical (initial) and to-be-marketed (current) formulations bioequivalent?

There were two bioequivalence studies conducted by the Applicant to compare 333 mg tablets: (a) a single dose crossover study and (b) a multiple dose crossover study. Additionally a multiple dose study was conducted to compare 333 mg and 500 mg tablets. The 333 mg vs. 500 mg tablet bioequivalence study was presumed to be conducted to support the US96.1 safety and efficacy study.

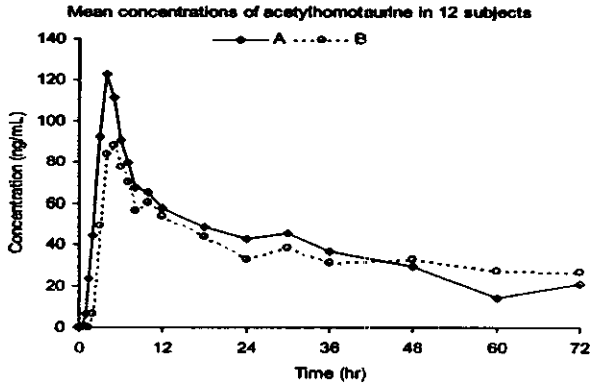
Single dose Study

This study was a randomized, a single dose, open-label, 2-period, crossover study in overnight fasted healthy male subjects. Treatments A and B were initial clinical and currently marketed formulations, respectively. As stated previously, 333 mg acamprosate tablet is currently marketed worldwide (Aotal and Campral). Bioequivalence was evaluated by comparing the 90% confidence intervals for the estimate of the ratio of the treatment geometric means with the bioequivalence region of [80%, 125%].

The data indicated that C_{max}, AUC_{last} and AUC_{0-24} did not meet the bioequivalence criteria. However, AUC_{∞} ratio fell within the bioequivalence limits. Additionally the analysis showed that a period effect was significant on all PK parameters. Generally this was due to insufficient washout period between administration.

The conclusion from this study was not surprising to this reviewer since enteric-coated tablets may generally show greater variability over conventional tablets due to the coating. Additionally two 333 mg tablets were administered rather than one 666 mg tablet. Consuming two tablets may further add to the variability. Further, the study does not seem to be adequately powered. Since acamprosate is intended for chronic administration, utilizing a schedule of multiple daily doses, this reviewer feels that extent of absorption is most relevant for acamprosate rather than the rate of absorption.

Overall, since the single dose bioequivalence study is considered to be the most sensitive to pick up formulation differences, this study showed that initial and currently marketed formulations were not bioequivalent.



Mean concentration of acetylhomotaurine, following single doses of reference formulation of acamprosate (A) and test formulation (B).

Comparison Of Pharmacokinetics Parameters In Fourtillan III: Single Dose Study Of Initial Formula And Current Formula

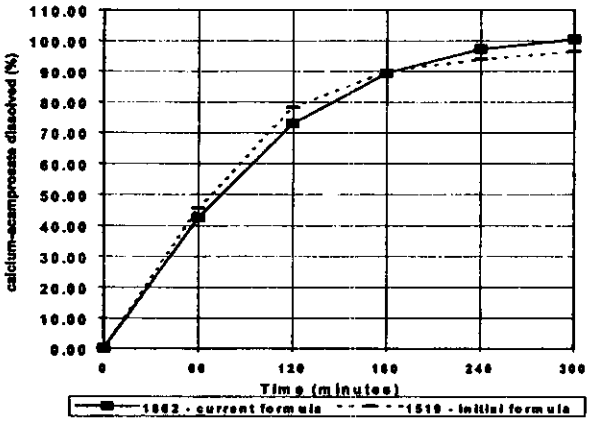
Parameter		Treatment	
		A (Initial formula or Reference formulation))	B (Current formula or Test formulation)
C_{max} (ng/mL)	N	12	12
	Geometric Mean	126.1	93.8
	95% Conf. Interval Limits	92.5, 172.0	72.0, 122.2
t_{max} (hr)	N	12	12
	Geometric Mean	4.0	5.0
	95% Conf. Interval Limits	3.0, 12.0	3.0, 10.0
$t_{1/2}$ (hr)	N	12	9
	Geometric Mean	20.0	22.1
	95% Conf. Interval Limits	13.3, 30.1	15.4, 31.8
AUC_{last} (ng/mL*hr)	N	12	12
	Geometric Mean	2352.9	2074.6
	95% Conf. Interval Limits	1814.6, 3050.8	1552.6, 2772.2
AUC_{∞} (ng/mL*hr)	N	12	9
	Geometric Mean	2988.8	2290.0
	95% Conf. Interval Limits	2210.4, 4041.3	1738.6, 3016.4

Confidence Intervals of the Ratios of Parameters Used to Assess Bioequivalence:
(A = reference formulation; B = test formulation)

Parameter	Geometric Mean Ratio (B/A)	Standard Error	Lower 90% Confidence Limit	Upper 90% Confidence Limit
C_{max} (ng/mL)	0.744	1.118	0.607	0.911
AUC_{last} (ng/mL*hr)	0.882	1.059	0.795	0.978
AUC_{0-24} (ng/mL*hr)	0.815	1.033	0.769	0.864
AUC_{∞} (ng/mL*hr)	0.978	1.058	0.878	1.089

Comparative Dissolution of Initial and Current Formulations

The comparative dissolution profiles of the two batches, No.1519 (initial formula) and No.1862 (current formula), are presented in below figure. It appears that both formulations exhibited similar dissolution profiles.

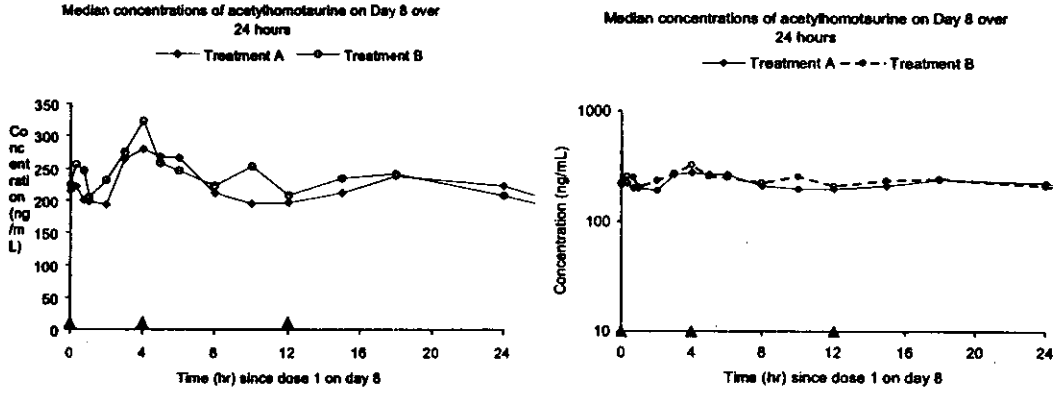


The dissolution testing was performed using a rotating basket apparatus at 180 rpm, at 37°C, in a pH 6.8 buffer solution.

Multiple dose study

This study was a randomized, open-label, 2 period, multiple dose (three times daily for 8 days), crossover study. This study was conducted due to the complications observed in the single dose study (a significant period effect and Cmax failure in single dose bioequivalence testing). Trough concentrations were analyzed and compared (Days 6, 7 and 8) as well as acamprosate concentrations on Day 8.

There were no significant differences between the 2 formulations in pharmacokinetic parameters.



Pharmacokinetic profiles (left, linear scale; right, semi-log scale) following a 24 hour dosing interval with initial formulation (Treatment A) and current formulation (Treatment B)

Comparison Of Pharmacokinetics Parameters In Fourtillan V: Multiple Dose Study Of Initial Formula and Current Formula

Parameters		Treatment	
		A (Initial formula or Reference formulation))	B (Current formula or Test formulation)
C_{max-ss} (ng/mL)	N	16	16
	Geometric Mean	358.6	352.6
	95% Conf. Interval Limits	283.1, 454.3	286.9, 433.3
$t_{1/2}$ (hr)	N	16	13
	Geometric Mean	16.8	18.1
	95% Conf. Interval Limits	12.1, 23.3	13.1, 24.9
AUC_{τ} (ng/mL*hr)	N	16	16
	Geometric Mean	5771.7	5904.5
	95% Conf. Interval Limits	4565.1, 7297.3	4817.6, 7236.8
AUC_{last} (ng/mL*hr)	N	16	16
	Geometric Mean	10806.91	11382.14
	95% Conf. Interval Limits	8901.9, 13119.6	9050.6, 14314.2
AUC_{∞} (ng/mL*hr)	N	16	13
	Geometric Mean	12162.5	11960.4,
	95% Conf. Interval Limits	10000.5, 14791.8	9580.8, 14931.0

Confidence Intervals of the Ratios of Parameters Used to Assess Bioequivalence:
(A = reference formulation; B = test formulation)

Parameter	Geometric Mean Ratio (B/A)	Standard Error	Lower 90% Confidence Limit	Upper 90% Confidence Limit
Cmax (ng/mL)	0.983	1.107	0.822	1.176
AUC last (ng/mL*hr)	1.053	1.099	0.892	1.244
AUC 0-24 (ng/mL*hr)	1.023	1.109	0.853	1.227
AUC infinity (ng/mL*hr)	1.010	1.105	0.845	1.208

Is 666 mg three times daily dosing comparable to 500 mg two times daily dosing?

Theodor I study was a randomized, open-label, 2-way crossover with no washout between two dosage forms. The crossover from the first to second treatment occurred on Day 10. Each treatment lasted for 9 days. The Applicant stated that two formulations appear to be equivalent at steady-state acamprosate concentrations. This reviewer conducted a cursory review of this study to assess the extent of acamprosate absorption. The data indicated that the extent of acamprosate absorption is similar between two formulations at steady-state acamprosate concentrations. This reviewer concurs with the Applicant's conclusion.

Investigations of differences between the 2 treatment conditions were done by comparing the first pharmacokinetic days of each condition, i.e., Treatment $B_{Day\ 8+17}$/Treatment $A_{Day\ 8+17}$ or the second days, i.e., Treatment $B_{Day\ 9+18}$/Treatment $A_{Day\ 9+18}$. The analysis was conducted by adding the two days since there were no carry-over effects observed. Additionally comparison of the ratio of pooled $AUC_{0\text{-}24(ss)}$ data of Treatment B versus that of Treatment A, i.e., Treatment $B_{Day\ 8+9+17+18}$/Treatment $A_{Day\ 8+9+17+18}$ and determining the 90% Confidence Intervals were conducted.

Pharmacokinetic Parameters at Steady State with Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

PK Parameter	Min	Max	Median	Mean
	TREATMENT A: Day 8 + Day 17 (n = 23)			
$AUC_{0-24(ss)}$ (ng.h/mL)			5903.71	7364.83
$C_{max(ss)}$ (ng/mL)			458.30	522.85
$T_{max(ss)}$ (h)			4	7.07
$C_{min(ss)}$ (ng/mL)			111.00	174.46
$C_{ave(ss)}$ (ng/mL)			245.99	306.87
Ptf			1.08	1.24
	Day 9 + 18 (n = 23)			
	Min	Max	Median	Mean
$AUC_{0-24(ss)}$ (ng.h/mL)			6008.10	6884.43
$C_{max(ss)}$ (ng/mL)			448.50	471.48
$T_{max(ss)}$ (h)			5	8.96
$C_{min(ss)}$ (ng/mL)			105.00	156.24
$C_{ave(ss)}$ (ng/mL)			250.34	286.85
Ptf			1.10	1.18
	Day 19 to 23 (n= 10)			
	Min	Max	Median	Mean
$t_{1/2}$ (h)			15.53	17.00
	TREATMENT B: Day 8 + 17 (n = 23)			
	Min	Max	Median	Mean
$AUC_{0-24(ss)}$ (ng.h/mL)			6523.53	6691.95
$C_{max(ss)}$ (ng/mL)			411.40	481.09
$T_{max(ss)}$ (h)			4	7.22
$C_{min(ss)}$ (ng/mL)			141.40	144.29
$C_{ave(ss)}$ (ng/mL)			271.81	278.83
Ptf			1.20	1.30
	Day 9 + 18 (n = 23)			
	Min	Max	Median	Mean
$AUC_{0-24(ss)}$ (ng.h/mL)			5983.55	6204.05
$C_{max(ss)}$ (ng/mL)			456.70	481.16
$T_{max(ss)}$ (h)			4	9.48
$C_{min(ss)}$ (ng/mL)			110.40	139.39
$C_{ave(ss)}$ (ng/mL)			249.31	258.50
Ptf			1.08	1.46
	Day 9 to 23 (n = 9)			
	Min	Max	Median	Mean
$t_{1/2}$ (h)			2.29	13.68

Ptf: Peat to trough ratio

Comparison of Steady State [$AUC_{0-24(ss)}$] Following Either Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

$AUC_{0-24(ss)}$	Mean Ratio (%)	90% Confidence Interval (%)		Bioequivalence Accepted
		Lower Limit	Upper Limit	
$A_{Day\ 8+17}/A_{Day\ 9+18}$	103.65	91.00	118.06	Yes
$B_{Day\ 8+17}/B_{Day\ 9+18}$	110.18	96.72	125.50	Yes
$B_{Day\ 8+17}/A_{Day\ 8+17}$	90.99	79.88	103.64	Yes
$B_{Day\ 9+18}/A_{Day\ 9+18}$	85.60	75.15	97.50	No

Comparison of Steady State C_{max} Following Either Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

$C_{max\ (ss)}$	Mean Ratio (%)	90% Confidence Interval (%)		Bioequivalence Accepted
		Lower Limit	Upper Limit	
$B_{Day\ 8+17}/A_{Day\ 8+17}$	92.70	79.55	108.02	Yes
$B_{Day\ 9+18}/A_{Day\ 9+18}$	98.64	82.18	118.40	Yes

Is the proposed dissolution testing acceptable?

The Applicant stated that Method "B", below, was used in the development of the product in the U.S. and will be used for the release and stability testing on batches intended for the U.S. market. Additionally the Applicant stated that this "B" method fully meets the requirements described in USP24-NF19 (Monograph <711> and <724>, delayed release tablets).

The "B" method makes use of the following operating parameters:

- **Equipment type:** [ ]
- **Medium:**
  - Acid stage: [ ]
  - Buffer stage: pH 6.8 [ ] 37°C ± 0.5°C
- **Speed of rotation:** [ ]
- **Sampling time:** [ ]
- **Analytical method:** Assay of calcium-acamprosate by HPLC after direct detection using UV absorption.
- **Dissolution specifications** (% of calcium acamprosate dissolved):
  - [ ] %
  - pH 6.8 buffer 120 min [ ] %.

This reviewer feels that additional dissolution data may be needed to validate the methodology proposed by the Applicant. Therefore, the following information request was communicated to the Applicant:

a) Justification of using Method B over Method A;
b) Dissolution data from 333 mg enteric-coated "current" formulation tablet lot(s) used in pharmacokinetic studies using the proposed method, Method B (e.g., Lot # 1862 from BE study, etc.);
c) Justification of using [ ]: Are there any data from other speeds, [ ]
d) Justification for using pH 6.8; Are there any data at other pH values,
e) Justification of proposing acid solution when is actually measured;
f) Justification of proposing 120 minutes as a single time point for the buffer solution; Are there any data at time-points earlier than 120 minutes, e.g., 30, 60, etc.?

4.6 Analytical

Is overall acamprosate analytical methodology acceptable?

This reviewer found two basic methods used to determine acamprosate in biological fluids, an HPLC method and a GC-MS method. Either HPLC or GC-MS method was used in individual studies. This reviewer did not find any critical deficiencies in the overall acamprosate analytical methodology to warrant any comments or additional information from the Applicant. See below a brief description for HPLC and GC-MS methods.

a. Determination of acamprosate by HPLC Fluorimetric and Electrochemical Detection

According to the Applicant, in the mid-1980s, an HPLC method [ ] was developed. With this method, the plasma sample was [ ]

The [ ] Quantitation was made by a fluorescence detection [ ] and an electrochemical detector [ ] The lower limit of quantitation (LLOQ) was approximately 5 to 10 ng/mL in plasma, and approximately 200 ng/mL in urine. Precision and accuracy of this method was acceptable.

b. [ ]

A gas chromatographic detection method was developed in 1990 [ ] The Applicant stated that this basic method is the reference method and is referred to as the method of choice for the determination of acamprosate in complex biological fluids. After [ ]

[ ]

[ ]

ng/mL. The accuracy and precision of the method were acceptable [ ] In February 1998, the method was re-validated using current ICH guidelines. In June 1998, the internal standard was changed to [ ]. The assay was again re-validated

[ ]

5 Labeling

The labeling proposed by the Applicant will be the subject of a separate review. A dosage adjustment for subjects with insufficient renal function needs to be included in the Dosage and Administration section of the package insert.

9 page(s)
of draft labeling
redacted from the
approval package

6.2 Individual Study Reviews

The individual study reports are attached below.

125/89391 (Chasseaud): Pharmacokinetics and Metabolism of 35S-AOTA-Ca following Oral Administration of Single Doses to Two Human Subjects

125/89391 (Chasseaud) was an open-label study conducted at [redacted] June 29, 1988 to July 28, 1988) in which 2 healthy male volunteers received single oral doses of ^{35}S-acamprosate (^{35}S-AOTA-Ca), as an aqueous solution. The study was conducted and the analytical work performed under the supervision of [redacted] The clinical portion of the study was carried out [redacted]

The objectives of the study were to determine the extent of absorption of acamprosate through measurement of plasma and whole blood concentrations of radioactivity, and to obtain information about the metabolism of acamprosate, the rates and routes of excretion of radioactivity, and the extent of plasma-protein binding of radioactivity and of acamprosate. The two male subjects were 34 and 37 years of age, respectively.

A batch of ^{35}S-acamprosate of specific activity 0.031 µCi/mg was prepared. A single oral dose was administered, containing approximately 1320 mg acamprosate. Subjects were confined to the clinical unit from 12 hours before dosing until at least 48 hours after dosing.

Samples of whole blood were taken before dosing and at regular intervals up to 120 hours after dosing and processed for plasma assays. Samples of urine and feces were collected over the same period. Radioactivity was assessed by liquid scintillation counting. Chromatographic study of selected samples was performed with thin-layer chromatography (TLC), using calcium acetylhomotaurine (Aota-Ca) or homotaurine as reference standards and high performance liquid chromatography (HPLC).

Significant concentrations of radioactivity were detected in plasma samples from the time of first blood sampling (15 minutes post-dose) until 24 hours later, with maximum radioactivity in plasma at 2 hours in one subject and at 0.5 hours post-dosing in the other (maximum values of — and — µg equiv./mL, respectively). Decline in plasma radioactivity was log-linear, with half-life of about 5 hours. No significant radioactivity could be detected in whole blood, although there were some technical limitations based on available sample volumes.

The excretion of radioactivity in the urine of Subject 1 (33.83% of the administered dose) was more significant than in Subject 2 (19.52% of the dose), with the major portion excreted during the first 24 hours, post-dosing. The major route of excretion of radioactivity was fecal, accounting for about 60% of the dose, and considered to represent unabsorbed drug (based on thin-layer and HPLC of methanol extracts of feces, which detected only N-acetylhomotaurine).

N-acetylhomotaurine was also present in urine samples from both subjects, together with homotaurine in varying proportions, which, according to the investigators, possibly represented metabolic deacetylation of acamprosate. Pooled plasma samples from the 2 volunteers were extracted and chromatographed and also showed the presence of chromatographic peaks consistent with homotaurine and N-acetylhomotaurine.

Plasma protein binding was considered to be negligible, after study by equilibrium dialysis against phosphate-buffered saline, in ex vivo samples from the 2 subjects and in pre-dosing samples incubated in vitro with 11 µg ^{35}S-Aota-Ca.

During the study, one of the subjects experienced nausea with insertion of the indwelling venous catheter, and was anorectic during the remaining days of the study, but this was not thought to be directly related to the drug. Otherwise, there were no significant problems.

In conclusion, this study showed that absorption of oral acamprosate solution was relatively low, that the majority of the absorbed dose was eliminated as the parent drug via the urinary route, and that fecal radioactivity, which was high, represented unabsorbed drug. In addition, it was demonstrated that there was no significant protein binding of acamprosate.

[ ]7488 (Scott): The Metabolism and Pharmacokinetics of ^{14}C Aota-Ca in Man; [ ] 7646 (Scott): Analysis of the Major Radioactive Components in Urine and Faeces from Rats and Man Following Oral Administration of [^{14}C] Aota-Ca (Acamprosate)

[ ]7488 (Scott) was an open-label study conducted by [ ] October 31, 1990) in which 4 healthy male volunteers received single oral doses of 1320 mg of ^{14}C-radiolabelled acamprosate (^{14}C-Aota-Ca), as an aqueous solution. The objectives of the study were to assess the absorption, distribution, metabolism, and excretion of radioactivity. This study was a complementary study that analyzed the radioactive components in urine and feces from the study subjects. The Study Director, responsible for the clinical conduct of the study, [ ] and the analytical work was under the supervision of [ ]

The subjects were 4 males, ages 33-41 years (mean: 36.8 years), with body weights ranging from 55 to 88.2 kg (mean: 72 kg) and heights from 163.4 to 176.3 cm (mean: 170.8 cm). Subjects were confined to the [ ] from the evening prior to dosing until 120 hours (5 days), post-dosing.

An oral solution of acamprosate (batch no. 3011, [ ] g) was combined in approximately 115 mL aqueous solution with ^{14}C acamprosate (Lot No. 89355). The specific activity of the solution was 1.325 kBq.mg^{-1}. Each volunteer received 25 mL of the solution (1320 mg).

Blood samples were withdrawn at regular intervals for a total of 120 hours post-dosing to determine total radioactivity. Portions of the blood were retained as whole blood and the remainder processed for plasma assay. Samples of urine and feces were collected over each 24 hour period for 5 days post-dosing. Total radioactivity was measured in each sample. In addition, radioactive components from pooled urine and fecal samples were analyzed by HPLC and TLC.

Only limited absorption of acamprosate solution was apparent, with the apparent maximum concentration of plasma radioactivity occurring between 1 and 2.5 hours post-dosing, in the range of 0.54–2.05 µg equiv.mL^{-1}. However, because the concentrations of radioactivity were close to or at background levels, interpretation of the data was difficult.

Excretion via the urinary route accounted for a mean of 11.0% of the administered radioactivity. A mean of 88.2% of administered radioactivity was recovered from the feces with 3 of the 4 subjects excreting a mean of 94.4% of the administered radioactivity over 120 hours.

Radio-HPLC analysis of pooled urine and fecal samples from the subjects indicated the presence of a single major radiocomponent with a retention time similar to that of ^{14}C-acamprosate. No significant peak with a retention time similar to homotaurine was observed. In addition, radio TLC analysis of urine and fecal samples similarly showed only a single peak in 2 different solvent systems, without evidence of homotaurine.

In general, the test drug was well tolerated. There were no significant changes in any hematologic or clinical chemistry parameter or electrocardiographic recordings. Three of the 4 subjects experienced minor adverse events, including light-headedness in 2 subjects and nausea and abdominal pain in a third subject.

In conclusion, in this study there was low absorption of the radiolabeled acamprosate solution, with only about 11% of the administered radioactivity recovered in the urine, as unchanged acamprosate. The remainder was recovered in the feces and was thought to represent unabsorbed drug. There was no evidence of metabolism of ^{14}C-acamprosate. Specifically, there was no evidence of homotaurine.

ACAMP/F/98.02 (Caplain): Pharmacokinetic Study Following Intravenous Infusion of 333 mg of Acamprosate to Assess the Pharmacokinetic and Elimination Parameters of Acamprosate

ACAMP/F/98.02 (Caplain) was an open-label, one period study conducted [ ] (Sept. to Dec., 1998) which assessed the pharmacokinetics of a single intravenous dose of unlabelled acamprosate in 12 young healthy male volunteers. The objectives of the study were to assess the pharmacokinetic and elimination parameters of acamprosate following a single intravenous infusion of 333 mg (concentration of 150 mg/10 mL), given over 15 minutes, in the fasting state. [ ] Analytical work was performed by [ ]

The 12 male subjects ranged from 20 to 38 years of age (mean = 25.6 years), with body weights ranging from 62.8 to 99.2 kg (mean = 72.8±9.0 kg) and heights ranging from 168.0 to 185.0 cm (mean = 175.4±5.4 cm).

The study was conducted in an inpatient clinical research unit. Subjects were admitted to the unit 24 hours prior to the study and remained in the unit for at least 72 hours following the infusion. Subjects were given standardized meals during their stay in the unit and water intake was controlled at 1600 mL/day on Days -1 and 1 and 1500 mL/day on Days 2 and 3.

Following an overnight 10-hour fast, a 22.2 mL intravenous infusion containing 333 mg acamprosate (150 mg/10 mL) was given over a 15 minute period on Day 1.

Samples of whole blood were taken before dosing (T0) and then at frequent intervals over the ensuing 24 hours (18 additional samples, including samples at 5, 10, 15, 25 and 45 minutes, post-dose). Urine samples were also collected at intervals (0-2h, 2-4h, 4-8, 8-12h, 12-24h, 24-48h, 48-72h) over 72 hours, post-dose. Samples were assayed for acamprosate by a GC-MS method. Pharmacokinetic parameters measured included C_{max}, T_{max}, AUC, total clearance (CL_T), renal clearance (CL_R), non-renal clearance (CL_{NR}), volume of distribution (Vd), total amount of administered drug excreted in the urine (Ae), elimination rate constant (k_e), and the terminal plasma half-life ($t_{1/2}$) of acamprosate. Descriptive statistics of pharmacokinetic parameters are summarized in below table.

Pharmacokinetic analysis showed that interindividual variability of the pharmacokinetic parameters of acetylhomotaurine was small (25% for C_{max}, 18% for both AUCs and 5% for Ae). C_{max} had a mean (±SD) of 27,870±6,92 ng.mL^{-1} and always occurred at the end of the 15 minute infusion. Thereafter, the plasma concentration declined with a terminal elimination half-life of 5.7±2.8 hours. The median value for this parameter was 4.67 hours. The amount of acetylhomotaurine excreted in the urine during the 72 hours post-infusion ranged from [ ] to [ ] mg (mean: 347.5±18.3 mg). Difficulty in achieving precise measurements of urine volume of collected fractions and coefficient of variation of the analytical method may have accounted for recovery of more than 100% of the administered dose in some subjects. These results, however, indicated that renal excretion was the sole route of elimination of acamprosate, following intravenous infusion.

Mean (±S.D.), CV (%), Minimum and Maximum Values of Pharmacokinetic Parameters after Intravenous Administration of 333 mg Acamprosate

Pharmacokinetic Parameter*	Mean (±S.D.)	C.V. (%)	Min.-Max
C_{max} (ng/mL^{-1})	27,869 (6,916)	25	
T_{max} (h)	0.25 (-)	-	
AUC_{0-t} (ng.h/mL)	24,832 (4,411)	18	
$AUC_{0-\infty}$ (ng.h/mL)	24,876 (4,427)	18	
$t_{1/2}$ (h)	5.7 (2.8)	49	
Ae (mg)	347.5 (18.3)	5	
Cl_T (L/h)	13.8 (2.7)	20	
Cl_R (L/h)	14.4 (2.9)	20	
Vd (L)	109.5 (41.7)	38	

Values based on data from 12 subjects
General safety and tolerability of the study medication were good. No serious adverse events were reported. Minor and occasional out of range values for selected vital signs were not considered to be of clinical significance. There were no significant effects on electrocardiographic findings.
It was concluded that, under the study conditions, a 333 mg dose of acamprosate infused intravenously over 15 minutes, was well tolerated. Pharmacokinetic results showed low inter-individual variability for key parameters, in contrast to the oral route where inter- as well as intra-subject variabilities are very high. Renal excretion of unchanged drug was virtually 100% by 8 hours post-infusion, substantiating that renal excretion was the sole route of elimination of acamprosate when administered as a 15 minutes intravenous infusion. Finally, this analysis provided further evidence that there is no metabolism of acamprosate.

RD 298/17927 (Dewland II): A Rising Dose Tolerance and Pharmacokinetic Study of Calcium Bis Acetyl Homotaurine Following Single Oral Administration of a Solution at Four Dose Levels

RD 298/17927 (Dewland II) was a non-randomized, single-blind, 4-part, single dose/rising dose pharmacokinetic study of acamprosate oral solution which was conducted at [ ] The clinical portion was performed from March 13, 1990 to April 13, 1990, under the direction of Principal Investigator Dr. Peter M. Dewland, MB, BS, Bsc, Dip Pharm Med.

The objectives of the study were to determine concentrations of acetylhomotaurine in plasma and urine following single oral doses of acamprosate solution and to monitor the tolerance of increasing doses of the study medication, as well as the incidence of adverse events. The analytical portion of the study was also performed by [ ]

Six healthy male volunteers, ages 26-37 years (mean age: 29.5 years), with body weights ranging from 51 to 87.9 kg (mean: 68.45 kg) and heights ranging from 1.64 to 1.85 m (mean: 1.73 m), participated in the study. Subjects reported to the Clinical Pharmacology Unit [ ] the evening prior to dosing and remained confined to the unit until 48 hours, post-dosing, for each study period.

Single doses of an oral solution of acamprosate were administered at 7 day intervals, following an overnight fast, at the following dose levels: 333 mg, 666 mg, 1332 mg, and 2664 mg.

Blood and urine were collected at set time intervals over a 48 hour period following the administration of each dose level of acamprosate. Plasma and urine samples were assayed for acetylhomotaurine using a GC-MS method.

Pharmacokinetic parameters at the various doses are shown in below Table 1.

There appeared to be a good linear correlation between C_{max} and oral dose (R^2 = 0.9401) and between AUC and oral dose (R^2 = 0.9906, excluding the 333 mg dose level). T_{max} results indicated that the absorption rate of the drug was not affected by dose. At the lowest dose, the mean half-life of acetylhomotaurine was 2.0 h, however, at the 666 mg, 1332 mg and 2664 mg dose levels the mean half-life values were 13.0 h, 12.5 h and 14.5 h, respectively. This difference may be explained by a limitation of analytical sensitivity at the limit of detection (approximately 10 ng/mL).

Pharmacokinetic Variables Following Oral Solutions of Acamprosate

Acamprosate Dose Level in mg (Number of Subjects)	Mean (SD) Value of Variable at Various Dose Levels of Acamprosate Oral Solution					
	C_{max} (ng/mL)	T_{max} (h)	AUC_{∞} (ng-h /mL)	K (h^{-1})	$t_{1/2}$ (h)	CL_R (L/h)
333 (n = 6)	325.9 (143.3)	1.42 (0.2)	1155.4 (657.8)	0.401 (0.164)	2.0 (0.7)	23.8 (16.6)
666 (n = 6)	782.8 (257.4)	1.5 (0.5)	5442.5 (1888.0)	0.056 (0.015)	13.0 (3.2)	7.7 (2.3)
1332 (n = 6)	914.0 (316.0)	1.4 (0.5)	7196.9 (2316.8)	0.060 (0.018)	12.5 (3.7)	12.9 (3.5)
2664 (n = 6)	1549.5 (744.3)	1.2 (0.5)	12624.2 (5265.0)	0.050 (0.013)	14.5 (3.4)	16.9 (7.6)

At acamprosate doses of 333 mg, 666 mg, 1332 mg, and 2664 mg, the percentage of administered dose that was excreted unchanged in the urine was, respectively, 4.9-6.8% (333 mg), 4.1-8.2% (666 mg), 5.3-7.8% (1332 mg), and 4.1-9.9% (2664 mg). Mean renal clearance (CL_R) values in L/h at the 333 mg, 666 mg, 1332 mg, and 2664 mg dose levels were as follows: 23.798; 7.742; 12.913; and 16.865. These values suggested that renal tubular secretion contributed to drug elimination.

Solutions of acamprosate given as single oral doses of up to 2664 mg were well tolerated and resulted in an apparent linear increase in the observed maximum plasma concentration and amount absorbed, with increasing dose. T_{max} values were unaffected by dose and occurred at approximately 1.4 hours. The high renal clearance suggested that there was a component of renal tubular secretion in study drug elimination, in addition to glomerular filtration.

SS 409 (Theodor II): Double-Blind, Placebo-Controlled, Multiple Rising Dose Bioavailability Study to Determine Tolerability, Safety and Pharmacokinetic Parameters under Steady State Conditions of Four Acamprosate Treatments (300 mg vs. 50 mg vs 800 mg vs 1000 mg Acamprosate Administered b.i.d. as an Oral Aqueous Solution) in Four Groups of 15 Healthy Male Volunteers Each

SS 409 (Theodor II) was a randomized (within group), double-blind, placebo-controlled, 4-dose level, sequential, multiple dose, rising dose pharmacokinetic and tolerability study of various doses of acamprosate oral solution. The study was conducted at [redacted] Oct. 25, 1994 to Dec. 19, 1994, under Principal Investigator, Dr.med. Rudolf A. Theodor. The analytical portion of the study was performed by [redacted]

Sixty-two normal, healthy, adult male volunteers participated in this sequential study of 4 different dose levels (Treatments A-D) of acamprosate solution. Sixty completed their assigned treatment period (15 per dose level). In Group III (Treatment C group), 1 volunteer withdrew consent (No. 307) and 1 volunteer (No. 312) was administered the wrong treatment on a single occasion and was, therefore, replaced. Replacements were, respectively, No. 357 and No. 362.

In Group I (Treatment A), the 15 volunteers ranged in age from 18 to 40 years (mean age: 27.9 years), with body weights ranging from 59.8 to 82.9 kg (mean weight: 72.0 kg) and heights ranging from 162 to 186 cm (mean height: 176.3 cm). In Group II (Treatment B), the 15 volunteers ranged in age from 18 to 39 years (mean age: 26.5 years), with body weights ranging from 58.5 to 97.0 kg (mean weight: 72.4 kg) and heights ranging from 169 to 195 cm (mean height: 178.2 cm). In Group III (Treatment C), the 17 volunteers ranged in age from 19 to 40 years (mean age: 27.2 years), with body weights ranging from 55.8 to 83.8 kg (mean weight: 70.4 kg) and heights ranging from 169 to 192 cm (mean height: 177.1 cm). In Group IV (Treatment D), the volunteers ranged in age from 20 to 37 years (mean age: 29.7 years), with body weights ranging from 60.8 to 86.5 kg (mean weight: 72.7 kg) and heights ranging from 170 to 192 cm (mean height: 179.5 cm).

The study design provided for sequential initiation of the 4 treatment groups, 15 subjects per group. Within each group, 12 subjects were randomly assigned to active treatment and 3 to placebo. Each group was to be dosed for 8 days, beginning with the lowest dose group. At 14 day intervals, the remaining groups were sequentially initiated, providing the preceding lower dose seemed to be safe. Subjects received the various doses of oral acamprosate solution twice daily (q12h) for 8 consecutive days. The 4 treatment groups were as follows:

Group I (Treatment A): 300 mg/10 mL b.i.d. for 8 days (600 mg/day);
Group II (Treatment B): 500 mg/10 mL b.i.d. for 8 days (1000 mg/day);
Group III (Treatment C): 800 mg/10 mL b.i.d. for 8 days (1600 mg/day);
Group IV (Treatment D): 1000 mg/10 mL b.i.d. for 8 days (2000 mg/day).

The volunteers were confined to the [redacted] center unit for approximately 10 days, starting from approximately 14 hours before the first scheduled dosing until after the final blood withdrawal following the last dose of study medication on Day 8. Thereafter, additional blood withdrawals were performed on an outpatient basis. In general, volunteers were fasted over night for 0h blood samples and meals were served approximately 30 minutes after dosing.

Acetylhomotaurine levels in blood and urine were assayed by a validated GC-MS method.

Mean pharmacokinetic parameter results are shown in below tables.

Steady state appeared to be reached at Day 6 for Treatments A, B, and C. For Treatment D (1000 mg b.i.d.), there was a significant decrease in mean trough plasma concentration from Day 6 to 7 and then a non-significant increase from Day 7 to Day 8.

There was no statistically significant difference between treatment groups for renal clearance. Mean terminal half-life ($t_{1/2}$) ranged from 13.47 hours to 17.47 hours. No significant difference was detected between treatment groups for this parameter or for T_{max}.

Terminal Half-Life and Renal Clearance at Steady State, Following Multiple Doses of Oral Acamprosate Solution, Administered to Healthy Volunteers: Mean (SEM) Values

	Treatment Groups			
	Treatment A (300 mg b.i.d.) n = 12	**Treatment B (500 mg b.i.d.) n = 12**	**Treatment C (800 mg b.i.d.) n = 12**	**Treatment D (1000 mg b.i.d.) n = 12**
t1/2 (h)	17.47 (2.76)*	13.47 (2.15)**	15.99 (2.13)	16.92 (2.13)
CL_R (mL/min)	229.51 (23.50)	269.76 (39.06)	267.55 (23.87)	205.39 (14.80)

* For this parameter, n = 9.
** For this parameter, n = 10.

Pharmacokinetic Parameters Following Multiple Doses of Oral Acamprosate Solution, Administered to Healthy Volunteers: Mean Values and Comparisons

Pharmacokinetic Assessment	**Dose Levels***				**Linearity Tests**	
	Treatment A (300 mg b.i.d.) n = 12	**Treatment B (500 mg b.i.d.) n = 12**	**Treatment C (800 mg b.i.d.) n = 12**	**Treatment D (1000 mg b.i.d.) n = 12**	**A, B, C, D**	**A, B, C**
$C_{max(ss)}$ (ng/mL)	378.37	566.48	804.47	751.70	p<0.1	NS
$C_{max(ss)}$ proportional to dose	1.000	0.898	0.797	0.596	p<0.1	NS
$T_{max(ss)}$ (h)	171.15	170.48	171.83	172.35	NS	NS
$T_{max(ss)}$ proportional to dose	1.000	0.996	1.004	1.007	NS	NS
AUC (ng.h/mL)	3254.48	4883.36	7744.85	7736.01	NS	NS
AUC proportional to dose	1.000	0.900	0.892	0.713	NS	NS

* At each dose level, subjects received 2 unit doses per day (b.i.d., q12h).

Subjects tolerated the 4 acamprosate solution doses well. In conclusion, in this rising dose study of multiple doses of acamprosate oral solution (600, 1000, 1600, and 2000 mg/day), steady state was reached by Day 8 in all treatment groups, and by Day 6 for the first 3 groups. $C_{max(ss)}$ and $AUC_{0-24(ss)}$ increased in a linear manner with increasing dose for the first 3 groups, but at the dose level of 800 mg b.i.d., there appeared to be a plateauing and linearity was not confirmed. There were no statistically significant differences in renal clearance, $t_{1/2}$, or $t_{max(ss)}$ for any of the dose groups. Except for a higher incidence of flatulence, loose stools and headache in the active group, relative to the placebo group, the treatment assignments were well tolerated.

Meram: February 6, 1991 (Jaillon) was a ***pilot*** randomized, double-blind, placebo-controlled, 4-way cross-over study of various single doses of intravenously administered acamprosate, which was conducted by [redacted] Prof. P. Jaillon, MD. The objectives were to determine the pharmacokinetic parameters of various intravenous doses of acamprosate and their linearity. Analytical work was performed by [redacted]

The subjects were 12 healthy male volunteers, ages 18 to 28 years (mean age: 23 years), with body weights ranging from 59 to 78 kg (mean: 71 kg) and heights ranging from 1.73 to 1.85 m (mean: 1.80 m).
In this 4 period study, each subject was randomly assigned to receive a dose of intravenous acamprosate or placebo at weekly intervals. All 12 subjects received all 4 treatments. The doses given were 10 mg/kg, 20 mg/kg, 30 mg/kg acamprosate or placebo (0.9% sodium chloride solution). Study medication was given at 8 AM by intravenous pump over 10 minutes. Subjects were confined to the hospital for 24 hours post-dosing.
Blood samples were withdrawn up to 24 hours after administration of study drug. Urine samples were collected for 24 hours, post-dosing.
Levels of acetylhomotaurine were determined using a HPLC assay.
Pharmacokinetic parameters are shown below.

Mean (±SD) Pharmacokinetic Values for Plasma and Urine Following Intravenous Acamprosate (Jaillon) N=12

	Dose mg	C_{max} mg/L	AUC_{0-t} (mg.h/L)	$AUC_{0-\infty}$ (mg.h/L)	Total CL l/h.kg	U_{∞} mg	U%	Renal CL L/h.kg
10 mg/kg	710.83 (52.82)	41.75 (11.51)	33.23 (19.41)	43.36 (22.58)	0.33 (0.20)	618.55 (222.92)	89.08 (36.78)	0.25 (0.13)
20 mg/kg	1421.67 (105.64)	88.08 (19.15)	83.08 (25.60)	93.76 (29.14)	0.24 (0.11)	1250.83 (321.69)	88.23 (23.05)	0.21 (0.10)
30 mg/kg	2132.50 (158.47)	139.25 (26.89)	159.13 (54.46)	172.02 (58.71)	0.19 (0.05)	1906.80 (447.95)	89.70 (20.77)	0.16 (0.04)

The maximum concentration (C_{max}) values increased linearly with dose (R=0.88), as did the areas under the curves (AUC_{∞}) (R=0.79), although one subject (Subject 2) had unusually high AUC values at the 30 mg/kg dose compared to the 10 mg/kg dose (approximately 8 times).
The urinary excretion of acamprosate (U_{∞}) over 24 hours increased significantly as a function of dose (p=0.0001). The percentage of acamprosate excreted unchanged in the urine (U%) did not vary significantly with the dose (p=0.99) and represented around 90% of the administered dose.
Excluding Subject 2 from the calculations, total clearance did not differ between doses of 10 and 30 mg/kg (p=0.0777). Renal clearance did not differ significantly with dose (p=0.15).
There was no evidence of injection site intolerance. After single intravenous acamprosate infusions of doses ranging from 711 mg to 2132 mg; pharmacokinetic response for C_{max} and AUC was linear. With all 3 dose levels, 90% of the administered dose was eliminated unchanged in the urine during the initial 24 hours.

AD 875 H (Fourtillan II) was a non-randomized, open-label, 3 sequential period study of acamprosate, comparing the pharmacokinetics after dosing with oral tablets and intravenous dosing, conducted at the [redacted] from October 10, 1989 to August 27, 1990, with analytical work under the direction of Prof. J.B. Fourtillan, [redacted]

The objectives were to evaluate the pharmacokinetics of oral acamprosate, following a single dose and at steady state, and also to assess the absolute bioavailability of acamprosate, by comparing pharmacokinetics of intravenous and orally administered acamprosate.
Twenty-four healthy male volunteers participated in the study. They ranged in age from 20 to 35 years (mean age: 27 years) and had body weights ranging from 59 to 78 kg (mean: 69.5 kg) and heights ranging from 169 to 186 cm (mean: 177.4 cm).
The treatment sequences were as follows:
(Treatment 1) Oral administration of two 333 mg tablets of acamprosate (666 mg), given with 150 ml of tap water.
(Treatment 2) At least 14 days later, commencement of a multiple-dose period, consisting of two 333 mg tablets of acamprosate given with 150 ml of tap water at 08:00 AM, noon and 8:00 PM (1998 mg/day) for 7 days, with a final dose at 08:00 AM on Day 8.
(Treatment 3) At least 17 days later, a 15 minute intravenous infusion of 666 mg acamprosate.
Subjects were confined in the clinic from the evening preceding Treatment 1 until the morning after the dosing day; from the evening preceding the first dose of Treatment 2 until the morning of Day 2; from the evening of Day 6 through Day 8; and from the evening preceding Treatment 3 through Day 2. Subjects reported to the clinic for each dose during Treatment 2.
After the initial single dose, blood samples were withdrawn up to 72 hours and urine was collected for 96 hours. During the multiple dose phase, blood samples were withdrawn at regular intervals on Days 1, 6, and 7 and for up to 72 hours after the final dose on Day 8. Urine samples were collected at set intervals on Days 1 and 7. Following the intravenous infusion, blood samples were withdrawn over a 72 hour period and urine was collected for 96 hours.
Plasma and urine acetylhomotaurine levels were measured by a GC-MS method. The limit of detection with this method was 1 ng/mL.
A comparison of the pharmacokinetic results obtained after single-dose oral tablets and intravenous acamprosate is shown below. Following a single oral dose of 666 mg acamprosate (two 333 mg tablets), the absolute bioavailability coefficient (F) showed a mean value of 0.11 (±0.01). Despite such low bioavailability, plasma concentrations of acamprosate after a single oral dose of tablets were sustained over a prolonged period at a relatively high level and were higher than those observed after intravenous dosing from 12 hours post-dosing. The plasma decays during the terminal parts of the AUCs were also very different (32.7±4.3 hours with the oral dose vs. 3.2±0.2 hours with the intravenous dose).
Because plasma levels depend on mean residence time (MRT), which takes into account all the processes responsible for the pharmacokinetic handling of a drug in the body – namely, absorption, distribution, and elimination – the difference between the oral MRT (47.7±5.7 hours) and the intravenous MRT (1.54±0.03 hours) primarily reflects the kinetics of the absorption process (mean absorption time or MAT). As a consequence of this "flip-flop" phenomenon, acamprosate plasma concentrations were measurable for 48 hours. The mean absorption time (MAT) was 46.2±5.7 hours.
The volume of distribution, as reflected by Vd and Vss, and dependent on elimination half-life and MRT following intravenous dosing, reflected a moderate distribution in extravascular media, characteristic of a polar and poorly lipid soluble compound (sulfonic acid).
Following the intravenous dosing, the relative values of renal clearance (CL_R = 132±18 mL/min) and total clearance (CL = 263±12 mL/min) indicated that about 50% of the intravenous dose was recovered in the urine, unchanged.
In a previous study, (*Jaillon*), where acamprosate was administered intravenously, 90% of the dose was recovered unchanged in urine. To explain this discrepancy, a confirmatory study

(*Caplain*) was initiated with appropriate and standardized water intake and intensive monitoring of urine sample collection. Results of the *Caplain* study showed that acamprosate was indeed entirely (100%) excreted in urine as the unchanged product.

Acamprosate Pharmacokinetic Parameters Following a Single Oral Dose of Acamprosate Tablets (666 mg) and a Single Intravenous Dose of 666 mg in 24 Healthy Subjects (Fourtillan II)

Pharmacokinetic Parameters	**Oral Dosing (n = 24)**	**Intravenous Dosing (15 min. Infusion) (n = 24)**
Acamprosate Dose	666 mg (tablets)	666 mg (IV infusion)
C_{max} (ng/mL)	206 ± 23	38,819 ± 1,898
T_{max} (h)	5.2 ± 0.6	0.24 ± 0.05
$AUC_{0-\infty}$ (ng•h/mL)	4110 ± 442	39,696 ± 1737
$t_{1/2}\lambda z$ (h)	32.7 ± 4.3	3.2 ± 0.2
MRT (h)	47.7 ± 5.7	1.54 ± 0.03
MAT (h)	46.2 ± 5.7	--
CL/F (mL/min)	2981 ± 253	--
CL (mL/min)	--	263 ± 12
$U_{0-96\ hrs}$ (% of administered dose)	5.4 ± 0.6	49 ± 5.4
CL_R (mL/min)	148 ± 11	132 ± 18
F	0.11 ± 0.01	--
V_{ss} (L)	--	24 ± 1

Values for pharmacokinetic parameters after 7 days of acamprosate tablets, given according to a schedule of 666 mg tid (8 AM, noon, and 8 PM), are shown below.

Mean Pharmacokinetic Parameters Following the Multiple Dose Phase (666 mg tid, 8AM, noon and 8 PM for 7 days) (Fourtillan II)

Parameter	**Mean value**
C_{max} (Day 7) (ng/mL)	608
Ratio of Day 7/Day 1 AUC0-24	2.48
CL/F (mL/min)	4191
$t_{1/2\lambda z}$ (h)	20.8

During multiple doses with acamprosate, plasma concentrations increased less than expected, based on considerations of the apparent terminal half-life following single dose acamprosate. The only adverse event noted in the study was "cutaneous intolerance" during the course of the intravenous infusion for Subject 03, necessitating that the infusion be discontinued at 14 minutes and 35 seconds, instead of the full 15 minutes. This was considered minor.
In conclusion, this study characterized the pharmacokinetics of various dosing strategies of acamprosate. Following a 666 mg single oral tablet dose, a C_{max} of 206±23 ng/mL was observed at a T_{max} of 5.2±0.6 hours. Absolute bioavailability was low, corresponding to a coefficient F equal to 0.11±0.01
With multiple oral dosing, 3 times daily, steady state was reached after 5 days. Acamprosate plasma concentrations increased less than predicted from terminal half-life considerations following a single dose.
On Day 8, the terminal half-life ($t_{1/2\lambda z}$) was calculated to be 20.8±2.9 hours, considerably less than that calculated following a single dose (32.7±4.3 hours). Apparent average total clearance at steady state, CL/F, equal to 4191±290 mL/min, was higher than that observed after a single dose (2981±253 mL/min).

In this study, it appeared that the clearance of acamprosate was balanced between renal and non-renal elimination of unchanged drug. Also, excretion of the parent drug in urine represented about 50% of the intravenous dose. This result was in contradiction with the result observed in the *Jaillon* study (Section 6.3.3.6) where 90% of the dose was recovered as unchanged in urine. This discordance remained unexplained. Nevertheless, it is important to consider that plasma and urine assays were carried out using different analytical methodologies. Thus, a 3rd confirmatory study (Section 6.3.1.3, *Caplain*), to evaluate the exact percentage of acamprosate eliminated as unchanged in the urine, was initiated. The results of that study showed that urine was the unique route of elimination for acamprosate, since 100% of the dose was recovered in urine as the unchanged drug.

AD993H (Fourtillan III): Bioequivalence Study of Two Oral Preparations of Acamprosate

AD993H (Fourtillan III) was a randomized, open-label, 2-period, crossover study comparing the pharmacokinetic parameters of 2 oral enteric-coated tablet formulations of acamprosate when given as a single dose. The 2 formulations included the reference formulation (representing the tablet formulation used in most of the European clinical research program, including the pivotal and supportive safety and efficacy studies), and the test formulation (representing the currently marketed tablet formulation). The study was conducted from Sept. 2 to Oct. 11, 1991 at the [ ] The clinical study was conducted under the [ ] Analytical work was performed by [ ] the direction of Prof. J.B. Fourtillan.

Twelve normal, healthy, male volunteers, ages 19-30 years (mean age: 24.7 years) and weighing between 55 and 77 kg (mean: 67.5 kg) and with heights between 169 to 183 cm (mean: 174.9 cm) participated in the study.

The 12 subjects were randomized, with a Latin Square design, to receive the following treatments with a 7-day washout period between treatments:

Treatment A (***reference formulation,*** *used in European clinical development program*), each subject received a single dose of 2 tablets of acamprosate 333 mg/tablet (666 mg) in the fasting state, of Batch #1519 (batch size of [ ] tablets).

Treatment B (***test formulation,*** *tablets currently marketed*), each subject received a single dose of 2 tablets of acamprosate 333 mg/tablet (666 mg) in the fasting state, of Batch #1862 (batch size of [ ] tablets).

Subjects reported to the clinical unit [ ] the evening prior to each dosing and remained at the clinic for 24 hours after dosing (i.e., until the morning of Day 2).

Blood samples were withdrawn up to 72 hours, post-dosing. Acetylhomotaurine was determined in plasma and urine by a GC-MS method.

To compare administered acamprosate formulations, statistical analysis was performed on key pharmacokinetic parameters by an analysis of variance (ANOVA) model which included terms for treatments, periods and subjects [C_{max}, AUC(t)] or by non-parametric Wilcoxon test (T_{max}, T_{lag}). After the ANOVA, the 95% symmetrical confidence interval of the differences in means of the formulations was calculated to test influences of administered form on bioavailability of acamprosate. Mean (SEM) values of pharmacokinetic parameters are shown below.

Mean ± SEM Pharmacokinetic Parameters Following A Single Dose (666 mg) of Either of Two Formulations of Acamprosate Tablets in Normal Volunteers (Fourtillan III)

Pharmacokinetic Parameters	Mean (SEM) Values According to Treatment Group		Statistical Test
	Reference Formulation (Treatment A) (n = 12)	Test Formulation (Treatment B) (n = 12)	
C_{max} (ng/mL)	141.1 (21.0)	101.7 (12.8)	p <0.05†
T_{max} (h)	5.1 (0.8)	5.4 (0.5)	NS††
T_{lag} (h)	1.8 (0.3)	2.5 (0.2)	NS††
AUC(t) (ng.h/mL)	2581 (325)	2316 (334)	p <0.05†

* = Reference formulation is the formulation used in the European clinical development program.
** = Test formulation is the currently marketed tablet formulation.
† = ANOVA (Westlake)
†† = Wilcoxon matched-pairs rank test

As noted in other studies, there was considerable inter-individual variation in values of parameters for both formulations of acamprosate. C_{max} was significantly higher in Treatment A compared to Treatment B (141.1±21.0 ng/ml vs 101.7±12.8 ng/ml, $p<0.05$). However, despite these differences, the AUC(t)s were not significantly different and the Westlake confidence intervals were within the acceptable limits (respectively equal to 20 and 24%).

It was concluded, at the time the study was performed, that the reference (Treatment A) and test (Treatment B) formulations of acamprosate were bioequivalent, based on AUC comparisons and considering that the drug is administered clinically 3 times daily. Both formulations were very well tolerated.

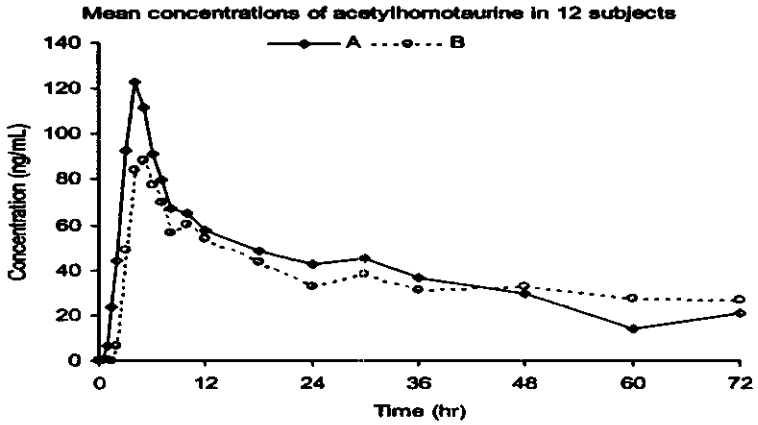
Addendum to Study Report: EMFFR2001/004/00 (EMF I)

Because Fourtillan III study was performed in 1991 and because the definition of bioequivalence and the requirements for demonstration of bioequivalence have evolved since then, data from this study were recently reanalyzed **(supplemental report EMFFR2001/004/00 [EMF I])**.
The maximum observed drug concentration (C_{max}) and the first time of its occurrence (T_{max}) were obtained directly from the concentration-time data. The time before start of absorption (T_{lag}) was also obtained directly from the concentration-time data: it is the time point immediately prior to the first quantifiable drug concentration. The area under the concentration-time curve from zero time (pre-dose) to a given time t (AUC_t), or to the time of last quantifiable concentration (AUC_{last}) was calculated by a combination of linear and logarithmic trapezoidal methods: the linear trapezoidal method up to C_{max} and the logarithmic trapezoidal method thereafter. The area from zero time to the last measurement time (AUC_{last}) is the sum of areas up to the last measurement time.

$$AUC_{\infty} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

The natural logarithms of the PK parameters C_{max}, AUC_{last}, and AUC_{∞} were analyzed using analysis of variance with sequence, subject within sequence [subject(sequence)], treatment, and period as factors. The results of the analysis of variance were presented, together with the antilogged least square means (geometric means), and the corresponding 95% confidence intervals. The results of the logarithms of the PK parameters and the corresponding 95% Confidence Intervals are presented in below table. Bioequivalence was evaluated by comparing the 90% confidence intervals for the estimate of the ratio of the treatment geometric means with the bioequivalence region of [80%, 125%]. The 90% confidence intervals for the ratio of the geometric means for the other PK parameters all exceeded the upper bioequivalence limit of 1.25: 90% confidence limits were C_{max}=[0.607, 0.911], AUC_{last}=[0.795, 0.978] and AUC_{0-24}=[0.769, 0.864]. However, the 90% confidence interval for AUC_{∞} ratio [0.878, 1.089] fell within the bioequivalence limits of 0.8 to 1.25.

The results of the analysis should be treated with caution since a period effect was significant on all PK parameters. It is possible that the washout period was insufficient to ensure lack of a period effect and data collected in Period 2 should, therefore, be ignored.
No statistical analysis of data collected in Period 1 only was performed, since the number of subjects was small (6 per treatment only) and the variability between subjects is known to be moderate to large for oral acamprosate. The mean plasma concentrations of acetylhomotaurine after single dose acamprosate (666 mg) are presented below for the reference (A) and for the test (B) formulations.



Mean concentration of acetylhomotaurine, following single doses of reference formulation of acamprosate (A) and test formulation (B).(Source: EMF I)

Comparison Of Pharmacokinetics Parameters In Fourtillan III: Single Dose Study Of Initial Formula And Current Formula

Parameter		Treatment	
		A (Initial formula or Reference formulation))	B (Current formula or Test formulation)
C_{max} (ng/mL)	N Geometric Mean 95% Conf. Interval Limits	12 126.1 92.5, 172.0	12 93.8 72.0, 122.2
t_{max} (hr)	N Geometric Mean 95% Conf. Interval Limits	12 4.0 3.0, 12.0	12 5.0 3.0, 10.0
$t_{1/2}$ (hr)	N Geometric Mean 95% Conf. Interval Limits	12 20.0 13.3, 30.1	9 22.1 15.4, 31.8
AUC_{last} (ng/mL*hr)	N Geometric Mean 95% Conf. Interval Limits	12 2352.9 1814.6, 3050.8	12 2074.6 1552.6, 2772.2
AUC_{∞} (ng/mL*hr)	N Geometric Mean 95% Conf. Interval Limits	12 2988.8 2210.4, 4041.3	9 2290.0 1738.6, 3016.4

Confidence Intervals of the Ratios of Parameters Used to Assess Bioequivalence:
(A = reference formulation; B = test formulation)

Parameter	Geometric Mean Ratio (B/A)	Standard Error	Lower 90% Confidence Limit	Upper 90% Confidence Limit
C_{max} (ng/mL)	0.744	1.118	0.607	0.911
AUC_{last} (ng/mL*hr)	0.882	1.059	0.795	0.978
AUC_{0-24} (ng/mL*hr)	0.815	1.033	0.769	0.864
AUC_{∞} (ng/mL*hr)	0.978	1.058	0.878	1.089

AD1044H (Fourtillan V): Comparative Study of Bioavailabilities of Two Oral Preparations of Acamprosate, During a Multiple Treatment by Doses Equal to 666 mg Given at 08.00, 12.00 and 20.00 for Eight Days

AD1044H (Fourtillan V) was a randomized, open-label, 2 period, crossover study comparing the pharmacokinetic parameters of two oral tablet formulations of acamprosate when given in multiple daily doses for 8 days. The two formulations included a reference formulation, representing the tablet formulation used in most of the European clinical research program (including the pivotal and supportive safety and efficacy studies), and the test formulation, representing the currently marketed tablet formulation. The study was conducted from July 16 to Sept. 26, 1992 . [ ] The clinical study was conducted [ ] Analytical work was performed by [ ] under the direction of Prof. J.B. Fourtillan.

Sixteen normal, healthy, adult male volunteers participated in the study. They ranged in age from 18 to 33 years (mean age: 24.2 years), with body weights ranging from 52 to 75 kg (mean: 66.0 kg) and heights ranging from 164 to 185 cm (mean: 175.8 cm).

The 16 subjects were randomized to receive the following treatments:

Treatment A (***reference formulation***, *used in European clinical development program*), each subject received two 333 mg tablets acamprosate at 8 AM, noon, and 8 PM for 8 days (i.e., 24 consecutive doses).

(Batch #1519 - Batch size of [ ] tablets).

Treatment B (***test formulation***, *tablets currently marketed*), each subject received two 333 mg tablets acamprosate at 8 AM, noon, and 8 PM for 8 days (i.e., 24 consecutive doses).

(Batch #1862 – Batch size of [ ] tablets).

During each of the 2 study periods, subjects were confined to [ ] from 12 hours prior to the first dose of acamprosate until 12 hours after the last dose of acamprosate on Day 8. Each morning dose (8 AM) was given after an overnight fast and subjects were not permitted fluids until 2 hours after this dose.

Blood samples were withdrawn just prior to the first dose of acamprosate and over the 24 hours following that dose. On Day 2, a blood sample was drawn at 18h and 24 h (just before Dose 4). Trough samples were collected on Days 6, 7, and 8. Blood samples were also withdrawn on Day 8 over the 72 hour period following the final dose.

Blood and urine samples were analyzed for acetylhomotaurine by a GC-MS method.

The mean values for these parameters are shown in In-Text Tables 6.3.5.3:1 and 6.3.5.3:2.

There were no significant differences between the 2 formulations in pharmacokinetic parameters characteristic of the bioavailability of acetylhomotaurine, including $AUC_{(0\text{-}24h)}$ on Day 1 and Day 8 and C_{max}, after each dosing on Days 1 and 8.

Only the areas under the curve between the 2 first consecutive dosings, $AUC_{(0\text{-}4h)}$ on Day 1, were significantly different when comparing results observed with the reference formulation, Treatment A, and the test formulation, Treatment B. It was considered that this related to the difference in lag times.

As noted above, since acamprosate dosing is 3 times daily, this seems to be of no clinical relevance. Based on these overall results, it was concluded that the 2 formulations were bioequivalent.

Pharmacokinetic parameters (C_{min}, C_{max}, T_{max}) of Acetylhomotaurine Following Multiple Oral Doses of 666 mg of Either of Two Formulations of Acamprosate Tablets to Normal Volunteers (Fourtillan V)

Pharmacokinetic Parameters		Treatment A Reference Formulation (Batch #1519) (n = 16)	Treatment B Test Formulation (Batch #1862) (n = 16)	Statistical Results
Minimum Plasma Concentrations (Cmin)		**Mean (±S.D.)**	**Mean (±S.D.)**	
Day 8				
C_{min}172h (ng/mL) *prior to Dose 23*		327.8 (151.1)	311.8 (109.8)	NS (26.0%)*
C_{min}180h (ng/mL) *prior to Dose 24*		241.6 (136.5)	270.7 (183.6)	NS (47.7%)*
C_{min}192h (ng/mL)		268.1 (131.3)	249.6 (116.9)	NS (33.7%)*
Peak Characteristics				
Day 1				
C_{max} (ng/mL)	*Dose 1*	132.8 (83.7)	95.0 (62.1)	NS (58.9%)*
T_{max} (h)	*Dose 1*	3.8 (0.4)	3.9 (0.3)	
C_{max} (ng/mL)	*Dose 2*	132.2 (53.2)	126.2 (56.1)	NS (25.9%)*
T_{max} (h)	*Dose 2*	3.5 (3.1)	3.75 (2.6)	
C_{max} (ng/mL)	*Dose 3*	206.6 (88.7)	161.0 (43.3)	NS**
T_{max} (h)	*Dose 3*	6.6 (4.0)	6.0 (3.8)	
Day 8				
C_{max} (ng/mL)	*Dose 22*	362.3 (186.9)	335.3 (110.0)	NS**
T_{max} (h)	*Dose 22*	3.6 (0.8)	2.8 (1.3)	
C_{max} (ng/mL)	*Dose 23*	333.3 (166.8)	367.9 (253.4)	NS (40.1%)*
T_{max} (h)	*Dose 23*	2.8 (2.5)	3.3 (2.4)	
C_{max} (ng/mL)	*Dose 24*	320.2 (127.9)	346.9 (309.6)	NS**
T_{max} (h)	*Dose 24*	6.6 (3.5)	8.1 (5.3)	

* = ANOVA (95% symmetrical Confidence Interval)
** = Friedman test

Pharmacokinetic parameters (AUC, Urinary Excretion) of Acetylhomotaurine Following Multiple Oral Doses of 666 mg of Either of Two Formulations of Acamprosate Tablets to Normal Volunteers (Fourtillan V)

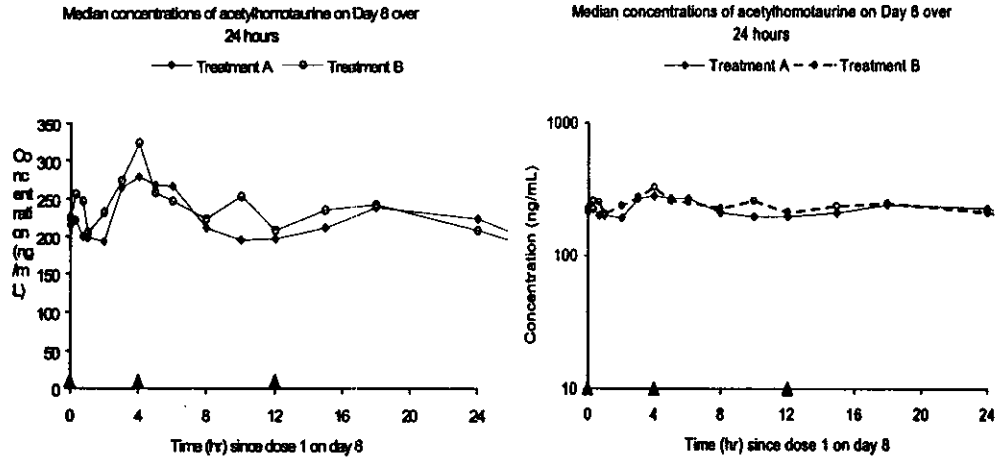
Pharmacokinetic Parameters	Treatment A Reference Formulation (Batch #1519) (n = 16)	Treatment B Test Formulation (Batch #1862) (n = 16)	Statistical Results
Area under the Curve (AUC) in ng.h/mL	**Mean (±S.D.)**	**Mean (±S.D.)**	
Day 1			
AUC (0-4h)	191.20 (110.89)	109.20 (78.63)	p<0.05*
AUC (4-12h)	699.19 (279.06)	725.96 (329.08)	NS (26.6%)*
AUC (12-24h)	1664.48 (631.15)	1485.18 (402.32)	NS (24.1%)*
AUC (0-24h)	2554.86 (928.01)	2320.35 (717.62)	NS (23.2%)*
Day 8			
AUC (168-172h)	1066.87 (525.84)	1062.49 (339.81)	NS (21.7%)*
AUC (172-180h)	2123.98 (987.33)	2393.51 (1432.90)	NS (26.7%)*
AUC (180-192h)	3158.14 (1483.66)	3290.47 (2104.51)	NS (25.8%)*
AUC (168-192h)	6348.99 (2896.58)	6746.47 (3810.50)	NS (23.3%)*

* = ANOVA (95% symmetrical Confidence Interval)

It was concluded that this comparative study of multiple doses of 2 formulations of acamprosate enteric-coated tablets (333 mg/tablet), the reference formula or Treatment A which was used in the European clinical development program and the test formula or Treatment B which is the currently marketed formulation, given according to the schedule of 2 tablets (666 mg) t.i.d. daily for 8 consecutive days, demonstrated that the formulations were bioequivalent, based on comparison of C_{max}, and $AUC_{(0-24)}$ on Days 1 and 8.

Addendum to Study Report: EMFFR2001/003/00 (EMF II)

Because the *Fourtillan V* study was performed in 1992 and because the definition of bioequivalence and the requirements for demonstration of bioequivalence have evolved since then, data from this study were recently reanalyzed (**supplemental report EMF II**). The methodology and conclusions of this reanalysis are summarized below.
The maximum observed drug concentration at steady-state (C_{max-ss}) and the first time of its occurrence (T_{max-ss}) were obtained directly from the concentration-time data. Because of the lag time before absorption, the minimum observed plasma concentration at steady-state (C_{min-ss}) may not coincide with C_τ. In that case, C_{min-ss} was determined as the minimum concentration occurring before absorption of the first dose of the day, i.e. during the first 4 hours. The pre-dose (trough) drug concentration (C_τ), where τ is the time at the end of the regular dosing interval, τ (i.e. 0 to 24 hr), was obtained directly or predicted from the concentration-time data.
The area under the concentration-time curve from zero time (pre-dose on Day 8) to the time of last quantifiable concentration (AUC_{last}) was calculated by a combination of linear and logarithmic trapezoidal methods. The area over the dosing interval (AUC_τ) was determined using the same methods. AUC_τ (in fact, AUC_{0-24}) was defined as the AUC for the whole duration of a regular dosing interval, i.e. 24 hours. The linear trapezoidal method was employed up to C_{max} and the logarithmic trapezoidal method was used thereafter. The area from zero time to the last measurement time (AUC_{last}) is the sum of areas up to the last measurement time.
The results of the logarithms of the pharmacokinetic parameters and the corresponding 95% Confidence Intervals are presented below table. The pharmacokinetic profiles of a 24 hour dosing interval at steady-state are displayed below, on linear and semi-log scales.



Pharmacokinetic profiles (left, linear scale; right, semi-log scale) following a 24 hour dosing interval with reference formulation of acamprosate (Treatment B) and test formulation (Treatment A) (Data Source: EMFR II)

The natural logarithms of the PK parameters C_{max}, AUC_{last}, AUC_{0-24} and AUC_∞ were analyzed using analysis of variance with sequence, subject within sequence [subject(sequence)], treatment and period as factors. Bioequivalence was evaluated by comparing the 90% confidence intervals for the estimate of the ratio of the treatment geometric means with the bioequivalence region of [80%, 125%] for the PK parameters C_{max}, AUC_{last}, AUC_{0-24} and AUC_∞.
Bioequivalence assessments based on the ratio of Test/Reference geometric means and associated 90% confidence intervals are presented in table below. For all parameters analyzed, the 90% confidence intervals fall entirely within the bioequivalence limits of 0.8 to 1.25. Thus, the results are consistent with the currently marketed or test (Treatment A) and initial or reference (Treatment B) formulations being bioequivalent at steady-state.

Comparison Of Pharmacokinetics Parameters In Fourtillan V: Multiple Dose Study Of Initial Formula And Current Formula

Parameters		Treatment	
		A (Initial formula or Reference formulation))	B (Current formula or Test formulation)
C_{max-ss} (ng/mL)	N Geometric Mean 95% Conf. Interval Limits	16 358.6 283.1, 454.3	16 352.6 286.9, 433.3
$t_{1/2}$ (hr)	N Geometric Mean 95% Conf. Interval Limits	16 16.8 12.1, 23.3	13 18.1 13.1, 24.9
AUC_{τ} (ng/mL*hr)	N Geometric Mean 95% Conf. Interval Limits	16 5771.7 4565.1, 7297.3	16 5904.5 4817.6, 7236.8
AUC_{last} (ng/mL*hr)	N Geometric Mean 95% Conf. Interval Limits	16 10806.91 8901.9, 13119.6	16 11382.14 9050.6, 14314.2
AUC_{∞} (ng/mL*hr)	N Geometric Mean 95% Conf. Interval Limits	16 12162.5 10000.5, 14791.8	13 11960.4, 9580.8, 14931.0

Confidence Intervals of the Ratios of Parameters Used to Assess Bioequivalence:
(A = reference formulation; B = test formulation)

Parameter	Geometric Mean Ratio (B/A)	Standard Error	Lower 90% Confidence Limit	Upper 90% Confidence Limit
Cmax (ng/mL)	0.983	1.107	0.822	1.176
AUC last (ng/mL*hr)	1.053	1.099	0.892	1.244
AUC 0-24 (ng/mL*hr)	1.023	1.109	0.853	1.227
AUC Infinity (ng/mL*hr)	1.010	1.105	0.845	1.208
Data Source: EMF II				

APPEARS THIS WAY
ON ORIGINAL

SS401 (Theodor I): Comparative Bioavailability Study to Compare Pharmacokinetic Parameters under Steady State Conditions of Two Acamprosate Treatments (666 mg Acamprosate T.I.D. vs 1000 mg Acamprosate B.I.D.) in 24 Healthy Male Volunteers

SS401 (Theodor I) was a randomized, open-label, 2-way crossover study comparing the pharmacokinetics of acamprosate at steady state using 2 multiple dose schedules and 2 different tablet strengths of acamprosate (two 333 mg initial tablets t.i.d. vs two 500 mg current tablets b.i.d.). Twenty-four normal, healthy, adult male volunteers participated in the study. The 24 subjects were randomized to receive each of the following treatments in this 2-way crossover study.

Treatment A: Each subject received two 333 mg tablets acamprosate 3 times daily, at 8 AM, noon, and 8 PM (total daily dose of 1998 mg) for 9 days (i.e., 27 consecutive doses) (Batch #0264).

Treatment B: Each subject received two 500 mg tablets acamprosate 2 times daily, at 8 AM and 8 PM (total daily dose of 2000 mg) for 9 days (i.e., 18 consecutive doses) (Batch #3432).

There was no washout period between treatments. The crossover from the first treatment to the second treatment for each volunteer, according to the randomization scheme, occurred on Study Day 10.

Pharmacokinetic parameters assessed included the following: 1) C_{max}, T_{max}, and AUC_{0-24} of the first 24 hours of dosing; 2) steady state assessment trough comparison of C_{min} of either Days 6, 7, and 8 or Days 15, 16, and 17; 3) maximum concentration of a 24 hour interval during steady state [$C_{max(ss)}$]; 4) time of maximum concentration of a 24 hour interval during steady state [$t_{max(ss)}$]; 5) average concentration of a 24 hour interval during steady state [$C_{ave(ss)}$]; 6) AUC of a 24 hour interval during steady state [$AUC_{0-24(ss)}$]; 7) apparent terminal plasma elimination half-life ($t_{1/2}$); and 8) urinary excretion [$Ae_{24(ss)}$]. Peak trough fluctuations (Ptf) were also assessed. These results are shown below.

Pharmacokinetic Parameters from First 24-Hour Treatment Interval with Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

PK Parameter	Treatment A (n = 12)		Treatment B (n = 11)	
	Mean (SEM) [Min-Max]	Median	Mean (SEM) [Min-Max]	Median
AUC_{0-24} (h.ng/mL)	1801.66 (216.59)	1698.88	2096.08 (479.37)	1573.70
C_{max} (ng/mL)	162.38 (21.50)	163.10	278.96 (88.49)	170.70
T_{max} (h)	15.25 (2.23)	15	18.55 (1.89)	18

In the statistical analyses of Day 1 variables (AUC_{0-24} and C_{max}), both comparisons failed to meet formal bioequivalence acceptance criteria, since the 90% confidence intervals were not within the range of 80% to 125%. For T_{max} of Day 1, no significant differences between Treatments A and B were found (Mann-Whitney, 2-sided non-parameter U-Test).

Comparison of Day 1 "Single Dose" Variables from First 24-Hour Treatment Interval with Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

Parameter	Comparison	Mean Ratio (%)	90% Confidence Interval (%)		Bioequivalence Accepted
			Lower Limit	Upper Limit	
AUC_{0-24}	B_{Day1}/A_{Day1}	102.77	66.98	157.69	No
C_{max}	B_{Day1}/A_{Day1}	138.25	85.21	224.32	No

The tablet strength (333 mg) and dose schedule for Treatment A is the one that was predominantly employed in the European clinical trials and the tablet strength (500 mg) and dose schedule for Treatment B was used in the American study, ACAMP/US/96.1

To investigate intraindividual variability of each treatment condition, the first pharmacokinetic day was compared to the second pharmacokinetic day (values from Day 8 and 17 and Day 9 and 18 were added since there were no carry-over effect and thus values were considered as independent.), e.g., Treatment $A_{Day\ 8+17}$/Treatment $A_{Day\ 9+18}$. Investigations of differences between the 2 treatment conditions were done by comparing the first pharmacokinetic days of each condition, i.e., Treatment $B_{Day\ 8+17}$/Treatment $A_{Day\ 8+17}$ or the second days, i.e., Treatment $B_{Day\ 9+18}$/Treatment $A_{Day\ 9+18}$. and by comparing the ratio of pooled $AUC_{0\text{-}24(ss)}$ data of Treatment B versus that of Treatment A, i.e., Treatment $B_{Day\ 8+9+17+18}$/Treatment $A_{Day\ 8+9+17+18}$ and determining the 90% Confidence Intervals.

Pharmacokinetic Parameters at Steady State with Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

	TREATMENT A: Day 8 + Day 17 (n = 23)			
PK Parameter	**Min**	**Max**	**Median**	**Mean**
$AUC_{0\text{-}24(ss)}$ (ng.h/mL)			5903.71	7364.83
$C_{max(ss)}$ (ng/mL)			458.30	522.85
$T_{max(ss)}$ (h)			4	7.07
$C_{min(ss)}$ (ng/mL)			111.00	174.46
$C_{ave(ss)}$ (ng/mL)			245.99	306.87
Ptf			1.08	1.24
	Day 9 + 18 (n = 23)			
	Min	**Max**	**Median**	**Mean**
$AUC_{0\text{-}24(ss)}$ (ng.h/mL)			6008.10	6884.43
$C_{max(ss)}$ (ng/mL)			448.50	471.48
$T_{max(ss)}$ (h)			5	8.96
$C_{min(ss)}$ (ng/mL)			105.00	156.24
$C_{ave(ss)}$ (ng/mL)			250.34	286.85
Ptf			1.10	1.18
	Day 19 to 23 (n= 10)			
	Min	**Max**	**Median**	**Mean**
$t_{1/2}$ (h)			5.53	17.00
	TREATMENT B: Day 8 + 17 (n = 23)			
	Min	**Max**	**Median**	**Mean**
$AUC_{0\text{-}24(ss)}$ (ng.h/mL)			6523.53	6691.95
$C_{max(ss)}$ (ng/mL)			411.40	481.09
$T_{max(ss)}$ (h)			4	7.22
$C_{min(ss)}$ (ng/mL)			141.40	144.29
$C_{ave(ss)}$ (ng/mL)			271.81	278.83
Ptf			1.20	1.30
	Day 9 + 18 (n = 23)			
	Min	**Max**	**Median**	**Mean**
$AUC_{0\text{-}24(ss)}$ (ng.h/mL)			5983.55	6204.05
$C_{max(ss)}$ (ng/mL)			456.70	481.16
$T_{max(ss)}$ (h)			4	9.48
$C_{min(ss)}$ (ng/mL)			110.40	139.39
$C_{ave(ss)}$ (ng/mL)			249.31	258.50
Ptf			1.08	1.46
	Day 9 to 23 (n = 9)			
	Min	**Max**	**Median**	**Mean**
$t_{1/2}$ (h)			12.29	13.68

Comparison of Steady State [$AUC_{0-24(ss)}$] Following Either Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

$AUC_{0-24(ss)}$	Mean Ratio (%)	90% Confidence Interval (%)		Bioequivalence Accepted
		Lower Limit	Upper Limit	
$A_{Day\ 8+17}/A_{Day\ 9+18}$	103.65	91.00	118.06	Yes
$B_{Day\ 8+17}/B_{Day\ 9+18}$	110.18	96.72	125.50	Yes
$B_{Day\ 8+17}/A_{Day\ 8+17}$	90.99	79.88	103.64	Yes
$B_{Day\ 9+18}/A_{Day\ 9+18}$	85.60	75.15	97.50	No
$B_{Day\ 8+9+17+18}/A_{Day\ 8+9+17+18}$	88.25	80.51	96.74	Yes

The intra-treatment comparisons of $AUC_{0-24(ss)}$ revealed the expected highly variable pharmacokinetic of acamprosate treatment seen in other clinical pharmacology studies, but were essentially bioequivalent. The overall comparison of pooled AUC data (Treatment $B_{Day\ 8+9+17+18}$/Treatment $A_{Day\ 8+9+17+18}$), the most important comparison, was fully contained within the required confidence interval range.

Comparison of $C_{max(ss)}$ between treatment conditions showed them to fulfill criteria of bioequivalence, based on 90% confidence intervals:

Comparison of Steady State C_{max} Following Either Treatment A (2X333 mg acamprosate t.i.d.) or Treatment B (2X500 mg acamprosate b.i.d.) in Healthy Volunteers

$C_{max\ (ss)}$	Mean Ratio (%)	90% Confidence Interval (%)		Bioequivalence Accepted
		Lower Limit	Upper Limit	
$B_{Day\ 8+9+17+18}/A_{Day\ 8+9+17+18}$	95.62	86.09	106.22	Yes
$B_{Day\ 8+17}/A_{Day\ 8+17}$	92.70	79.55	108.02	Yes
$B_{Day\ 9+18}/A_{Day\ 9+18}$	98.64	82.18	118.40	Yes

It was concluded that the 2 treatment schedules which employed 2 different strengths of identically formulated acamprosate enteric-coated tablets (333 mg and 500 mg), Treatment A with 666 mg t.i.d. and Treatment B with 1000 mg b.i.d., were pharmacokinetically equivalent. The safety and tolerability did not reveal any clinically relevant differences between the 2 treatment conditions: Treatment A, representing the "traditional" European dosing schedule (and the intended schedule for the current NDA application), and Treatment B, representing the dosing schedule used in the American randomized clinical trial, ACAMP/US/96.1. The results obtained demonstrated the clinical interchangeability of both treatment schedules, particularly in view of their intended chronic administration.

AD 1011H (Fourtillan IV): Influence of Food on Acetylhomotaurine Pharmacokinetics After Single Oral Administration of Acamprosate

AD 1011H (Fourtillan IV) was a randomized, open-label, 2-way crossover study of the effects of food on acamprosate (acetylhomotaurine) pharmacokinetics, conducted at the [ ] [ ] Analytical work was performed by . under the direction of Prof. J.B. Fourtillan. The clinical portion was performed between October 21, 1991 and November 17, 1991.

The objective of this study was to assess the influence of food on acetylhomotaurine pharmacokinetics after single dose administration of acamprosate tablets to healthy volunteers.

Twelve healthy male volunteers, ages 20-31 years (mean age: 24.8 years), with body weights ranging from 61 to 82 kg (mean: 72.3 kg) and heights ranging from 169 to 190 cm (mean: 180 cm) participated in the study.

The 12 subjects were randomized, with a Latin Square design, to receive the following treatments with a 7-day washout period between treatments:

666 mg acamprosate (two 333 mg reference formulation tablets) following an overnight fast of at least 10 hours, during which time only water was allowed, with the fast continuing for 2 hours, post-dosing;

666 mg acamprosate (two 333 mg reference formulation tablets), immediately following a standard meal.

Acetylhomotaurine was determined in plasma and urine by a GC-MS method.

The mean values for the pharmacokinetic parameters are shown below:

Effects of Food on Pharmacokinetic Parameters of Acamprosate (Fourtillan IV)

Dosing Condition of 666 mg Acamprosate Tablets (Number of Subjects)	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	$AUC_{(t)}$ (ng/mL·h)	$U_{(96)}$ (mg)	U (% of dose)
Fasting (n = 12)	171.75 (29.55)	9.58 (3.55)	2.37 (0.20)	2555 (257)	34.83 (2.29)	5.8 (0.4)
Fed state (n = 12)	99.30 (9.77)	6.92 (1.71)	2.68 (0.22)	1970 (221)	29.96 (2.70)	5.0 (0.4)
p-value	<0.05*	NS**	NS**	<0.05*	NS (27%)	--

* ANOVA (Westlake)

** Wilcoxon matched paired rank test

The maximum plasma concentrations of acetylhomotaurine (C_{max}) and the area under the curve (AUC) in the fasting state were significantly higher than in non-fasting subjects ($p<0.05$). For the other evaluated parameters, there were no statistically significant differences between the fasting and non-fasting states.

No adverse events or clinically significant changes in laboratory parameters were recorded.

It was concluded that the bioavailability of single dose acamprosate was significantly decreased when the study medication was administered with food. However, the clinical significance of this is considered to be minimal since acamprosate is intended for chronic administration, utilizing a schedule of multiple daily doses. In fact, the clinical efficacy and safety studies, all of which used t.i.d. dosing, instructed patients to take doses with meals.

RD 298/20673 (Dewland IV) was a study performed at the [redacted] from January 17, 1994 to March 28, 1994. Its objective was to compare the plasma pharmacokinetics of acamprosate following single dose oral administration of acamprosate tablets to equal numbers of men and women. The study was conducted under the direction of Principal Investigator Dr. Peter M. Dewland, MB, BS, Bsc, Dip Pharm Med. Analytical work was also done at [redacted]

Twenty-four healthy adult volunteers (12 male and 12 female) participated in the study. The 12 male volunteers were ages 24 to 46 (mean age: 32.1 years), with body weights ranging from 55.9-84.7 kg (mean weight: 69.2 kg), and heights ranging from 1.65-1.83 m (mean height: 1.74 m). The 12 female volunteers were ages 21 to 43 (mean age: 29.9 years), with body weights ranging from 53.7-88.5 kg (mean weight: 63.8 kg), and heights ranging from 1.56-1.76 m (mean height: 1.63 m).

Subjects received a single 666 mg dose of acamprosate tablets (two 333 mg tablets) following an overnight fast of at least 8 hours. Food, consisting of a light meal, was allowed 3 hours after dosing. Subjects were confined at the [redacted] from approximately 8 PM of the evening prior to dosing until 32 hours after dosing. They returned to the center for the remaining blood draws, up to 120 hours post-dosing.

Plasma acamprosate concentrations were determined by a validated GC-MS method.

Mean pharmacokinetic parameters of acamprosate for the female and male subjects are provided:

Mean (SD) Values for Pharmacokinetic Parameters for Female and Male Subjects Following A Single Oral Dose of Acamprosate Tablets (666 mg)

Pharmacokinetic Parameter	Mean (SD) for Females (n = 12)	Mean (SD) for Males (n = 12)	95% CI Difference	p-value
C_{max} (ng/mL)	212 (83)	188 (81)	(-45,93)	0.485
T_{max} (h)	4.25 (1.16)	4.96 (1.89)	--	0.280
$AUC_{0-\infty}$ (ng.h/mL)	3866 (2011)	3242 (2885)	(-1481, 2730)	0.545
AUCt (ng.h/mL)	3571 (1941)	2854 (2679)	(-1265, 2697)	0.461
$t_{1/2}$ (h)	28.4 (15.1)	27.5 (18.8)	(-13.6, 15.3)	0.903
λz	0.029 (0.012)	0.041 (0.031)	(-0.008, 0.031)	0.233
Log (Lz)*	-3.61 (-0.45)	-3.45 (0.75)	(-0.36, 0.69)	--
MRT (h)	40.6 (19.6)	36.5 (21.5)	(-13.2, 21.6)	0.624
AUMC (ng.h/mL)	170,275 (138,147)	148,010 (169,505)	(-108,648, 153,177)	0.728

* Lz data was transformed due to unequal variances of Lz for females and males.

As can be seen, there was no significant difference between male and female subjects for any acamprosate pharmacokinetic parameter.

Single oral doses of 666 mg acamprosate were well tolerated by both male and female subjects. There were no serious adverse events.

In conclusion, there were no significant differences in the plasma pharmacokinetics of acamprosate between male and female subjects following single dose oral administration of 666 mg of acamprosate tablets.

AOTA-CIN PA1-AD 1054H (Pelc III): Acamprosate Pharmacokinetic Study During the Treatment of Alcoholic Patients Following Withdrawal

AOTA-CIN PA1-AD 1054H (Pelc III) was an open-label study of multiple dose acamprosate in alcohol-dependent subjects. The study was conducted at [ ] [ ] from February 24, 1992 to December 7, 1992, under the direction of Principal Investigator, Dr. Isadore Pelc, [ ] [ ]

The study's objective was to determine the kinetics of acamprosate under therapeutic conditions of chronic dosing in alcoholic-dependent subjects, following their withdrawal from alcohol. Acamprosate analysis was performed by [ ] [ ]

Nine alcohol-dependent subjects, all of whom had been withdrawn from alcohol and had been abstinent for at least 5 days, participated in this study. Although the study was intended to be exclusively an in-patient study, in fact, 7 of the 9 subjects were in-patients only for the first week and then completed the study as out-patients. Seven of the subjects were men and 2 were women. Their ages ranged from 30 to 62 years (mean age: 41.9 years). Body weights ranged from 56 to 75 kg (mean weight: 64 kg) and heights ranged from 161 to 181 cm (mean height: 169.2 cm). All of the subjects had been alcohol-dependent for at least 2 years. During the month prior to the study, all the subjects had been on concomitant medication (7 of the 9 had been on diazepam) and 8 of the 9 subjects took other medications during the study (predominantly benzodiazepines).

Subjects received two 333 acamprosate tablets, 3 times daily, with meals, for a total daily intake of 1998 mg acamprosate, administered over 28 days.

Blood samples were obtained over 24 hours on Day 0 (first day of acamprosate treatment) and on treatment Days 7 and 28. On these days, acamprosate dosing was at 10 AM, 2 PM, and 8 PM. On Days 1 to 6, a blood sample was obtained at time 0, relative to dosing. Collected samples analyzed for acamprosate by a GC-MS.

No significant difference existed between the mean (±SD) values of $AUC_{(0\text{-}24h)}$ on Day 7 (9695±5126 ng.h/mL) and this same parameter on Day 28 (12,363±9995 ng.h/mL), although there was a great deal of variability between subjects. [ ] compared these data with those generated by their study of 24 healthy volunteers (*Fourtillan II*, described above), with the same daily dosing of acamprosate and concluded that the AUC at Day 7 in the normal healthy volunteers (8436±4307 ng.h/mL) was not significantly different from that seen in the current study in alcohol-dependent subjects (9695±5126 ng.h/mL).

Steady state was reached after 5 days of treatment, based on trough plasma levels (time 0).

In conclusion, in chronic alcoholic patients who have been withdrawn from alcohol, the mean plasma concentrations of acetylhomotaurine on the first and eighth day of dosing with acamprosate, 666 mg t.i.d. are similar to the concentrations observed in normal healthy volunteers, similarly dosed.

Steady state plasma concentrations were reached within approximately 5 days.

After a further 3 weeks dosing with acamprosate, there was a small but statistically non-significant increase in plasma concentrations of acetylhomotaurine compared with the values after 1 week.

AOTA-CIN IR1-AD 1033H (Sennesael) was an open-label study of acamprosate pharmacokinetics in subjects with renal impairment, conducted at [redacted] from February 1991 to August 1991, under the direction of Principal Investigator, Dr. J. Sennesael, MD.

The objective of the study was to evaluate the pharmacokinetics of acamprosate in healthy subjects and in patients with stable moderate to severe renal failure (creatinine clearance, respectively, in the range of 30-60 and 5-29 mL/min 1.73 m^2) after the administration of a single dose of acamprosate. Acamprosate analysis was performed by [redacted]

There were 18 subjects in the study. The 6 healthy volunteers (Group 1) were all males, ages 22 to 39 (mean age: 29 years), with body weights ranging from 58.4 to 84.7 kg (mean: 72.1 kg) and heights ranging from 169 to 180 cm (mean: 174.1 cm), and creatinine clearances ranging from 83 to 111 mL/min/1.73 m^2 (mean: 98 mL/min/1.73 m^2). Twelve adult outpatients with chronic renal failure comprised the 2 renal-impaired groups. The 6 patients with moderate renal impairment (Group 2) had the following demographic features: 3 were males and 3 were females; ages 36-67 (mean age: 56.8 years); body weights ranged from 54.5 to 80.4 kg (mean: 68.1 kg); and heights ranged from 158 to 178 cm (mean: 164.8 cm). Creatinine clearances ranged from 31 to 51 mLmin/1.73m^2 (mean: 41.0 mL/min/1.73 m^2). The 6 patients with severe renal impairment (Group 3) had the following demographic features: all were males; ages 34-69 (mean age: 51.2 years); body weights ranged from 67 to 81 kg (mean: 73.1 kg); and heights ranged from 158 to 178 cm (mean: 171.6 cm). Creatinine clearances ranged from 9 to 27 mLmin/1.73 m^2 (mean: 15.2 mL/min/1.73 m^2).

Each participant received a single oral dose of 666 mg acamprosate (two 333 mg tablets) along with 150 mL of water, following an overnight fast. Breakfast and usual medication (excluding antacids, H2-receptor antagonists, or resin) were permitted 2 hours after dosing.

Blood samples were collected at the following times, post-dosing: 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hrs. Urine samples were collected at 8-hourly intervals for 24 hours and then at 24 hourly intervals until 3 days after dosing. Plasma and urine samples were assayed for acamprosate by a GC-MS method.

Total apparent plasma clearance (Cl/F) and renal clearance (Cl_R) of acamprosate showed significant differences between the 3 groups, with reduction in both total clearance and renal clearance in subjects with renal impairment. The greatest reductions were seen in the group with severe renal impairment.

C_{max} and T_{max} were also significantly different between Groups 2 and 3 and between Groups 1 and 3. The plasma half-life ($t_{1/2}$) was significantly different only between Groups 1 and 3. C_{max} was highest in the severely renal-impaired group (Group 3) and T_{max} and $t_{1/2}$ were significantly longer in this group compared to either the control group (Group 1) or the group with moderate renal impairment (Group 2).

Although mean residence time (MRT) differences were not significant between the 3 groups, the mean values for this parameter increased from 28.14±3.45 h in Group 1 to 55.08±11.67 in Group 2 and 70.58±16.31 in Group 3. There was a negative correlation between the individual values for this parameter and the corresponding creatinine clearances: $R = 0.5186$; $p<0.05$.

The percent of administered drug eliminated in the urine was not significantly different between the 3 groups: 5.57±0.79% in Group 1, 4.26±0.63 in Group 2 and 6.19±0.76 in Group 3:

Mean (SEM) Pharmacokinetic Parameters (Sennesael)

	Group 1 Healthy Subjects	Group 2 Cr.Cl. 30-60 ml/min	Group 3 Cr.Cl. 5-29 ml/min	Statistics
C_{max} (ng/mL)	198±38	398±78	813±109	p<0.001**
	NS*	p<0.001	p<0.01	
T_{max} (h)	5.83±1.33	4.33±0.76	23.33±7.67	p<0.05†
	NS*	p<0.05*	p<0.05*	
$t_{1/2}$ (h)	18.21±3.21	33.35±6.58	46.62±12.85	p<0.05†
	NS*	p<0.05*	NS*	
MRT (h)	28.14±3.45	55.08±11.67	70.58±16.31	NS†
CL/F (L/h)	184.00±25.84	66.50±18.19	15.83±4.51	p<0.01†
	P<0.01*	p<0.01*	p<0.01*	
CL_R (L/h)	10.05±1.22	3.29±0.85	1.10±0.21	p<0.01†
	P<0.01*	p<0.01*	p<0.05*	
U %	5.57±0.79	4.26±0.63	6.19±0.76	NS**

* Mann and Whitney U test
** One-way ANOVA
† Kruskal-Wallis test

There was a linear correlation between individual values for creatinine clearance and the corresponding values for acamprosate: total apparent plasma clearance, CL/F ($R = 0.8235$; $p<0.001$); acamprosate renal clearance, CL_R ($R = 0.8932$; $p<0.001$), plasma half-life, $t_{1/2}$ ($R = 0.4666$; $p<0.05$) and mean residence time, MRT ($R = 0.5186$; $p<0.05$).
No side effects were reported nor were there any clinically significant changes in vital signs or electrocardiograms. Safety laboratory parameters were not modified as a result of administering acamprosate.
In conclusion, this study in renal-impaired subjects confirmed that the kinetics of acamprosate are linked to creatinine clearance and, therefore, to renal function. It also confirmed that the major route of elimination of the product is urinary and that any other mechanism, including metabolism, plays a negligible role. Finally, it suggested that prolonged dosing with the therapeutic dose of 3 x 2 tablets/day (acamprosate 1998 mg/day) would lead to accumulation of the drug in patients with impaired renal function, although the consequences of this, if any, are unknown.

90235 (Haug): Pharmacokinetic Study of Acamprosate Tablets (2 x 333 mg) in Patients with Different Stages of Impaired Liver Function Compared to a Control Group of Healthy Volunteers

90235 (Haug) was an open-label, in-patient study of the pharmacokinetics of acamprosate, following multiple oral doses, in subjects with varying degrees of hepatic impairment compared to healthy volunteers. It was conducted at

in May, 1991, under the direction of Dr. Gertaud Haug, MD. Analytical work was performed by

There were 18 subjects in the study (6 healthy subjects and 12 subjects with mild or moderate hepatic impairment). The 6 healthy volunteers were 5 males and 1 female, ages 46 to 54 (mean age: 50.5 years), with body weights ranging from 50.0 to 82.1 kg (mean: 74.2 kg) and heights ranging from 158 to 187 cm (mean: 175.5 cm). Four male and 2 female patients with mild hepatic insufficiency (Grade A, according to the Child-Pugh classification) were included. Their ages ranged from 37 to 62 years (mean age: 52.5 years) and their body weights ranged from 54.3 to 107.5 kg (mean: 69.2 kg) and heights ranged from 158 to 179 cm (mean: 167.7 cm). Six male patients with moderate hepatic insufficiency (Grade B, Child-Pugh classification) comprised the 3rd group. Their ages ranged from 44 to 55 years (mean age: 50.8 years) and their body weights ranged from 69.5 to 99.0 kg (mean: 86.5 kg) and heights ranged from 162 to 188 cm (mean: 171.8 cm).

To verify the degree of the hepatic insufficiency, patients received, intravenously, 1.2 mg of aminopyrine labeled with 1.5 µCi ^{14}C in order to conduct an aminopyrine breath test. In addition, sonography of the epigastric region was performed to confirm the diagnosis and the absence of extensive ascites.

In this open-label, multiple dose study, subjects were given two 333 mg tablets (666 mg/dose) of acamprosate three times daily (7 AM, noon, and 7 PM) for 7 days (1998 mg/day), with a single 666 mg dose on the morning of Day 8. The first dose on Day 1 was given after an 8 hour overnight fast and food was withheld until 2 hours after the first dose. For all other doses, subjects did not have food from 2 hours prior to dosing until 2 hours after drug administration, although water was allowed. Subjects remained in the clinical unit from the evening prior to the first study day until 24 hours after the last morning dose on Day 8.

Blood samples for acamprosate levels were obtained on Day 1 prior to the first dose and then up to 20 hours after the first dose; on Days 2 and 6 just prior to the first daily dose; on Day 7 prior to the first dose and then up to 20 hours after this dose; and finally, on Day 8 prior to the last morning dose and up to 96 hours after that last dose. Urine samples for acamprosate levels were collected over intervals of 12 hours on Days 6 and 7 following the morning and evening dosing. Plasma and urine acamprosate levels were measured by a GC-MS method.

The mean values for pharmacokinetic parameters are shown below. Variability of the calculated pharmacokinetic parameters was very high, but the mean values did not differ significantly between groups. Specifically, there were no statistically significant differences between the 2 groups of hepatic-impaired patients and the volunteer control group in the mean values at different days during this 1-week treatment period for C_{min}, C_{max}, T_{max}, the terminal rate constant (k), Ae, or AUCs from 0 to 24 hours, 0 to 5 hours, 5 to 12 hours, and Days 8 to 12.

As shown and defined in In-Text Table 6.3.7.5:1, the ratios A1, A2, and A confirm that, on average, plasma concentrations were higher on Day 7 than on Day 1, especially from hours 0 to 5. The mean values were similar for the patients with impaired hepatic function and the control group. The AUCs from Days 8 to 12, representing the elimination of the drug, were also not significantly different in healthy volunteers and hepatic-impaired patients. Standard deviations were high, especially in the patient groups, because of very high concentrations in 2 of the patients (Patient #10 and Patient #03) from Days 8 to 12.

Mean (SD) Values for Pharmacokinetic Parameters after Multiple Doses of Acamprosate: Healthy Volunteers Compared to Patients with Liver Impairment

Pharmacokinetic Parameter	Mean Values (± S.D.) for Subject Group			Statistical test
	Healthy volunteers (n = 6)	Mild liver impairment (n = 6)	Moderate liver impairment (n = 6)	
C_{min} (ng/mL)				
Day 2, H0	233±116	280±109	269±181	
Day 6, H0	449±280	397±125	472±278	NS
Day 7	265±187	146±105	287±324	
Day 8	158±95	123±109	271±363	
C_{max} (ng/mL)				
Day 1	360±66	352±134	388±120	
Day 7	644±386	588±241	683±508	NS
Day 8	534±195	556±317	601±601	
T_{max} (h)				
Day 1	15.3±6.4	16.8±9.3	13.7±8.7	
Day 7	7.3±4.4	13.7±11.6	9.3±10.0	NS
Day 8	3.5±0.5	3.8±2.1	6.2±5.1	
K (L/h)	0.056±0.012	0.074±0.052	0.053±0.025	NS
t ½ (h)	13.0±2.9	12.9±7.1	20.0±19.8	NS
AUC_{0-24h} (ng.h/mL)				
Day 1	3973±836	4046±2067	3596±836	NS
Day 7	9728±5491	7002±3822	10,957±10,398	
AUC_{0-5h} (ng.h/mL)				
Day 1	415±167	424±314	455±134	NS
Day 7	2456±1511	1826±1048	2564±1982	
AUC_{5-12h} (ng.h/mL)				
Day 1	1207±669	1211±813	904±493	NS
Day 7	3039±1726	1904±1138	2885±2777	
$AUC_{Day\ 6\text{-}Day12}$ (ng.h/mL)	11,019±6732	11,780±14,110	14,474±18,361	NS
A1 (AUC_{0-5h} at Day 7)/ (AUC_{0-5h} at Day 1)	6.4±4.4	7.4±6.9	6.2±4.7	NS
A2 (AUC_{5-12h} at Day 7)/ (AUC_{5-12h} at Day 1)	3.0±1.9	2.1±1.6	5.4±7.6	NS
A (AUC_{0-24h} at Day 7)/ (AUC_{0-24h} at Day 1)	2.4±1.3	2.0±1.5	2.9±2.3	NS
Ae (mg/24 h)				
Day 6	98.1±39.0	91.0±28.4	110.6±73.5	NS
Day 7	91.2±47.8	87.5±43.1	119.8±62.6	

The study drug was generally well-tolerated and all subjects completed the study. All adverse events were either mild or moderate and disappeared spontaneously. The healthy volunteers experienced more adverse events (18 events) than did the patients (14 events). There were no major differences in laboratory safety results and no significant changes in pre-study and post-study electrocardiograms.

In conclusion, following multiple dosing with acamprosate at the usual dosage schedule of 666 mg t.i.d. (1998 mg/day) in this single center study of normal healthy volunteers and patients with mild or moderate hepatic insufficiency, there was no evidence that impaired liver function affected the pharmacokinetics of acamprosate. There were no statistically significant differences in the mean values for C_{min}, C_{max}, T_{max}, AUC, or Ae between the 2 groups of hepatic-impaired patients and the volunteer control group, although inter-individual variability was high. The study drug was well-tolerated, with only mild or moderate adverse events which spontaneously resolved and which occurred with slightly greater frequency in the control group.

12/89-03 AL (Lücker): A Pilot Study of the Influence of Aotal on the Pharmacokinetics of Ethyl Alcohol

12/89-03 AL (Lücker) was a single-blind (subject), placebo-controlled, randomized, 2 period cross-over study of the pharmacokinetics of ethyl alcohol after either multiple doses of placebo or acamprosate (Aotal®). It was conducted at [redacted] in [redacted] Germany from April 24 to May 20, 1989. The principal investigator was P.W. Lücker, MD, Ph.D., FCP, Professor of Pharmacokinetics.

Twelve healthy, adult male volunteers participated in the study. They ranged in age from 22 to 34 years (mean age: 26 years) and had body weights ranging from 65.7 to 86.5 kg (mean weight: 76.3 kg) and heights ranging from 170 to 193 cm (mean height: 181.6 cm).

The volunteers reported to the inpatient unit 36 hours before the first administration of study drug and remained there for 5 days during each of the 2 study periods. There was a 1 week washout between study periods.

In the unit, volunteers were placed on a controlled dietary and fluid intake schedule. In a randomized crossover design, each volunteer received either acamprosate tablets or matching placebo tablets, 666 mg t.i.d. for 2 days (Days 2 and 3) with a single 666 mg dose at 8 AM on the following morning (Day 4), after an overnight fast. Two hours later, the volunteers were given 80 ml of 40% whiskey (approximately 32 grams ethanol) mixed with 80 ml of cold soda which was consumed within 30 seconds.

Blood samples were withdrawn on Day 4 of each study period at the following time points, relative to the whiskey (ethanol) administration: Pre-dose and 10, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after.

Ethanol concentrations were determined with the [redacted] Ethanol procedure, which had a detection limit of 0.01 mg/mL.

The median pharmacokinetic parameters of ethanol are shown in table below.

Pharmacokinetic Values (Median) for Single-Dose Ethanol after Pretreatment with Either Placebo or Acamprosate in Healthy Volunteers

	Median Values for Treatment Group	
Pharmacokinetic Parameter	**32 g ethanol after placebo pre-treatment**	**32 g ethanol after acamprosate pre-treatment**
C_{max} (µg/mL)	403.03	426.41
T_{max} (h)	0.75	0.75
AUC_{0-t} (µg.h/mL)	633.42	573.43

The pharmacokinetic parameters for ethanol did not differ significantly between the 2 pre-treatments.

There were no study drug-related changes in vital signs, electrocardiograms, or standard safety laboratory assessments. One volunteer had a slight elevation of SGPT (34.3 U/L, normal range of 2-22 U/L) after receiving acamprosate and ethanol, but this was not considered to be causally related to study drug.

In conclusion, the derived pharmacokinetic parameters for ethanol (C_{max}, T_{max} and AUC_{0-t}) in healthy volunteers following a single oral dose of approximately 32 g ethanol, consumed over 30 seconds, did not differ significantly in the presence or absence of acamprosate pre-treatment for several days, at a total daily dose of 1998 mg. Acamprosate was well-tolerated under the conditions of the study.

RD 298/17949 (Dewland III) was an open-label, randomized, 2 period cross-over study of the pharmacokinetics of a single oral dose of acamprosate in the presence or absence of ethanol. The study was conducted [redacted] United Kingdom from April 25, 1990 to May 22, 1990, under the direction of Principal Investigator Dr. Peter M. Dewland, MB, BS, Bsc, Dip Pharm Med. Analytical work was also performed by [redacted]

Twelve healthy, adult male volunteers participated in the study. They ranged in age from 19 to 38 years (mean age: 24.5 years) and had body weights ranging from 56 to 82.2 kg (mean weight: 68.0 kg) and heights ranging from 1.66 to 1.92 m (mean height: 1.77 m).

The 2 study periods were as follows:

Treatment 1: Single dose of four 333 mg acamprosate tablets (1332 mg) with ethanol (0.9 g/kg) given as a loading dose 1 hour prior to acamprosate, and 0.09 g/kg at time 0 and every 30 minutes thereafter for 7.5 hours.

Treatment 2: Single dose of four 333 mg acamprosate tablets (1332 mg) with orange juice given as an equal volume as the ethanol and at the same time periods.

Subjects reported to the clinical unit by 8 PM of the evening prior to dosing and remained in the unit until the 24 hours post-dosing blood sample had been taken. Thereafter, they returned to the unit for the remaining blood sampling (see below). There was a ≥7 day washout period between the 2 study periods.

Blood samples were taken for the determination of acetylhomotaurine prior to dosing and up to 48 hours. Breath alcohol was measured every 30 minutes for 8 hours and then every 4 hours until 24 hours after the acamprosate dose. Urine was collected pre-study and over 24 hours.

Acamprosate (acetylhomotaurine) levels were measured using a GC-MS method.

The mean (SD) and minimum and maximum values for the pharmacokinetic parameters, with and without alcohol are shown:

Mean (SD) Values for Acamprosate Pharmacokinetic Parameters in Normal Healthy Volunteers, Following A Single Oral Dose of Acamprosate (1332 mg), Either With or Without Alcohol

Pharmacokinetic Parameter	Mean (SD) (n = 12)	Minimum, Maximum	Statistical Test Untransformed (log transformed)
C_{max} (ng/mL)			
With alcohol:	288.97 (91.46)	[redacted]	p>F = 0.2234
Without alcohol:	257.68 (82.29)		(p>F = 0.1979)
T_{max} (h)			
With alcohol:	6.00 (4.07) [5.00]*	[redacted]	p>T = 0.2857**
Without alcohol:	7.83 (5.13) [7.00]*		
AUC_T (ng.h/mL)			
With alcohol:	5387.88 (2114.33)	[redacted]	p>F = 0.5374
Without alcohol:	5086.96 (1810.05)		(p>F = 0.7529)
AUC_∞ (ng.h/mL)			
With alcohol:	8894.33 (6536.59)	[redacted]	p>F = 0.7061
Without alcohol:	9573.28 (5135.99)		(p>F = 0.4121)
CL/F (L/h)			
With alcohol:	192.31 (118.17)	[redacted]	–
Without alcohol:	159.41 (78.27)		
$T_{1/2}$ (h)			
With alcohol:	30.84 (30.43)	[redacted]	75.9%†
Without alcohol:	46.75 (50.95)		
λz			
With alcohol:	0.04 (0.02)	[redacted]	–
Without alcohol:	0.03 (0.03)		

* = Median value
** = Wilcoxon Scores (Rank Sum)
† = Westlake 95% symmetrical confidence interval

Mean breath alcohol levels were sustained at a plateau level of approximately 80 mg/dL for almost 8 hours, post-acamprosate dosing.

The mean relative bioavailability of acetylhomotaurine from acamprosate without alcohol co-administration compared to with alcohol co-administration was 1.10 (S.E. 0.113) or 110.0% (95% CI: 85.2, 134.9). There were no statistically significant differences in C_{max}, T_{max}, AUC_T, or AUC_∞. These data are consistent with the conclusion that the rate and extent of absorption of acetylhomotaurine from acamprosate when given with alcohol were not statistically significantly different ($p>0.05$) from acamprosate given without alcohol.

In addition, the confidence limits of the bioequivalence parameters with alcohol co-administration were in the range of 90 to 130% of those derived from acetylhomotaurine without alcohol co-administration. The exception to this was the confidence intervals about the AUC means and the half-life means, which may have related to the high degree of variability between subjects and the limited number of subjects in the study.

In order to determine if homotaurine was a major metabolite of acetylhomotaurine, as had been suggested by an earlier radiolabeled study (*Chasseaud*), homotaurine levels were measured in plasma and urine samples from both study periods for a single subject (Subject 01). Inspection of the data showed that homotaurine levels were very low, most samples significantly less than 5.0 ng/mL, compared to the parent compound's C_{max} of approximately 214.0 ng/mL. Similarly, urinary levels were not greater than 0.011 µg/mL, whereas the lowest acetylhomotaurine urine level for this subject was 0.310 µg/mL and most samples ranged from 13.1 to 39.6 µg/mL. Based on these results, it was concluded that homotaurine was not a significant metabolite of acamprosate in man.

There were no serious adverse events. Five of the 12 subjects given 1332 mg acamprosate with alcohol suffered headaches which were probably due to the alcohol, since none of the subjects given the same dose of acamprosate with orange juice suffered headaches.

In conclusion, acamprosate tablets, given as a single oral dose of 1332 mg, were well tolerated, both with and without concomitant alcohol administration. The rate and extent of absorption of acetylhomotaurine with alcohol was not statistically significantly different from the rate and extent of absorption without alcohol. Confidence limits of the bioequivalence parameters, C_{max} and AUC_T, from the alcohol treatment period were in the range of 90 to 130% of those derived from acetylhomotaurine during the treatment period without alcohol. Finally, there was no evidence that homotaurine was a significant metabolite of acetylhomotaurine.

RD 298/20828 (Dewland V) was an open-label, randomized, 2 period cross-over study of the pharmacokinetics of acamprosate and disulfiram when given separately and concomitantly. It was conducted at the [ ] United Kingdom from September 12, 1994 to November 23, 1994, under the direction of Principal Investigator Dr. Peter M. Dewland, MB, BS, Bsc, Dip Pharm Med. Analytic work was also performed at [ ]

Twenty healthy, adult male volunteers participated in the study. They ranged in age from 20 to 41 years (mean age: 31 years) and had body weights ranging from 55.2 to 82.4 kg (mean weight: 70.8 kg) and heights ranging from 1.65 to 1.82 m (mean height: 1.73 m).
The 2 study periods were as follows:
Treatment 1: Two 333 mg acamprosate tablets 3 times daily (approximately, 9AM, 1PM, 8PM) for 14 days, with disulfiram (Esperal®), 500 mg (1 tablet) daily during Days 8 to 14, at approximately 9AM.
Treatment 2: Disulfiram (Esperal®), 500 mg (1 tablet) daily for 7 days, at approximately 9AM.
Subjects were confined to the Clinical Centre for the duration of each study period. There was a 14 day washout period between the 2 study periods.
Blood samples were taken for the determination of acamprosate on the following days and times during Treatment 1: Just prior to dosing only (time 0) on Days 1, 5, 6, 8, 12, 13, 16, 17, 18, and 19. On Day 7 and Day 14, samples were obtained frequently from time 0 to 16 hours. On Day 15, sampling was done at 0 and 6 hours, relative to dosing. Blood samples for the determination of the disfulfiram metabolites, diethyldithiocarbamate methyl ester (DDTC-Me) and diethylthiomethyl carbamate (DTC-Me) were obtained on the following days and time points: just prior to dosing only (time 0) on Days 8, 12, 13, 16, 17, 18, and 19. On Day 14, samples were obtained at intervals up to 16 hours post-dosing. On Day 15, sampling was done at 0 and 6 hours, relative to dosing.
During Treatment 2, blood samples for the determination of the disulfiram metabolites occurred at the following time points: just prior to dosing only (time 0) on Days 1, 5, 6, 9, and 10. On Day 7, samples were obtained at intervals up to 16 hours post-dosing. On Day 8, sampling was done at 0 and 6 hours, relative to dosing.
Plasma acamprosate was analyzed using a GC-MS method. It was intended to analyze for plasma metabolites of disulfiram using an HPLC-UV method, however, a failure with the assay precluded the latter analysis.
Below table shows the mean results for pharmacokinetic parameters during administration of acamprosate alone and with disulfiram:

Pharmacokinetic Parameters During Multiple Dosing of Acamprosate Alone or with Multiple Doses of Disulfiram (Dewland V)

Pharmacokinetic Parameter*	Acamprosate Alone (Day 7)		Acamprosate + Disulfiram (Day 14)	
	Mean	SD	Mean	SD
$AUC_{0\text{-}4h}$**	1059.58	511.76	1157.22	660.45
$AUC_{4\text{-}12h}$**	1955.08	768.51	2314.21	1078.45
$AUC_{12\text{-}24h}$**	2606.68	1166.33	2823.11	1688.20
$AUC_{0\text{-}24h}$**	5621.34	2343.16	6294.54	3113.32
C_{ss} (ng/mL)	234.22	97.63	262.27	129.72
C_{max} (ng/mL)	369.72	145.35	418.54	215.03
T_{max} (h)	5.45 (4.0)†	6.22	6.05 (5.0)†	5.74

* Values are based on data from all 20 subjects.
** Values for AUC are given as $ng \cdot mL^{-1} \cdot h$.
† Median is given in parentheses.

Comparison of the ratios (acamprosate/acamprosate + disulfiram) for these variables confirmed their equivalence. There were no statistically significant differences between the pharmacokinetics of acamprosate found on Day 7 after 7 days of dosing with acamprosate,

666 mg three times a day, and the pharmacokinetics of acamprosate on Day 14 after 14 days of dosing with acamprosate, 666 mg three times a day, plus disulfiram (500 mg), once daily from Day 8 to Day 14.

Acamprosate given as a dose of 666 mg three times a day (total daily dose, 1998 mg) was well tolerated, with few adverse events. Similarly, when co-administered with disulfiram, 500 mg/day, there were no serious adverse events and no increase in frequency of previously reported events. Additionally, when disulfiram, 500 mg/day, was administered for 7 days there were no serious adverse events.

In conclusion, because of the potential to use both acamprosate and disulfiram in patients with chronic alcoholism, it was of interest to explore the possibility of an interaction. Although they are processed differently by the body, they could have influenced the absorption of each other. The present study showed that concomitant administration of disulfiram with acamprosate in normal healthy volunteers does not result in any change in acamprosate pharmacokinetics. Because of analytical difficulties, it was not possible to assess if changes in disulfiram pharmacokinetics occurred.

APPEARS THIS WAY
ON ORIGINAL

AD 1126H (Decourt I): Research of Pharmacokinetic Interactions Between Diazepam and Acamprosate When Given in Combination on Multiple Oral Dosing

AD 1126H (Decourt I) was an open-label, randomized, 2 period cross-over study of the pharmacokinetics of acamprosate and diazepam when given alone and in combination. It was conducted at [ ] France from May 1, 1994 to August 21, 1994. The Principal Investigator was Dr. Jean-Philippe Decourt, MD [ ]. Analytical work was performed by [ ]

Seventeen healthy, adult male volunteers participated in the study. They ranged in age from 18 to 30 years (mean age: 23.6 years) and had body weights ranging from 57 to 80 kg (mean weight: 70.2 kg) and heights ranging from 165 to 191 cm (mean height: 179.3 cm). Sixteen of the subjects completed both study periods (see below).

The 2 study periods were as follows:

Period A: Diazepam (Valium®), 5 mg tablets twice daily (8AM and 8PM) for 14 days and two 333 mg acamprosate tablets t.i.d. (approximately, 8AM, noon, 8PM) from Days 8 to 14.

Period B: Two 333 mg acamprosate tablets (666 mg) t.i.d. (approximately, 8AM, noon, 8PM) for 7 days.

Subjects were confined to the study site from Day -1 to Day 15 of Period A and from Day -1 to Day 8 of Period B. There was a 10 day washout period between the 2 study periods.

During Period A, blood samples were taken just prior to the first diazepam dose on Day 1 and at the following time points on Day 7: just prior to Dose 13 of diazepam (time 0) and 1, 2, 4, 6, 8, 12 (just prior to Dose 14 of diazepam), 14, 16 and 24 hours (just prior to Dose 15 of diazepam and Dose 1 of acamprosate). On Day 14, blood samples were taken at time 0 (just prior to Dose 27 of diazepam and Dose 19 of acamprosate) and then at 1, 2, 4 (just prior to Dose 20 of acamprosate), 6, 8, 12 (just prior to Dose 21 of acamprosate and Dose 28 of diazepam), 14, 16 and 24 hours thereafter.

During Period B, blood samples were taken just prior to the first acamprosate dose and on Day 7, at the following time points: just prior to Dose 19 of acamprosate (time 0) and at 1, 2, 4 (just prior to Dose 20 of acamprosate), 6, 8, 12 (just prior to Dose 21 of acamprosate), 14, 16 and 24 hours.

Acamprosate plasma assays were performed using a GC-MS method. Diazepam and its main metabolite, nordiazepam, were assayed in plasma using an HPLC reversed phase method, with ultraviolet detection.

Below table compares mean values for pharmacokinetic parameters of diazepam and nordiazepam after 7 days of diazepam administration as monotherapy and after an additional 7 days (Day 14) with acamprosate co-administration:

Mean Values of Pharmacokinetic Values of Diazepam and Nordiazepam, When Given as Monotherapy and Co-administered with Acamprosate (Decourt I)

	Day 7 (Diazepam Alone) (n = 16)		Day 14 (Diazepam and Acamprosate) (n = 16)		Day 7/Day 14 (% of Day 14) (n = 16)	
Plasma Analyte	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)	$AUC_{(0-24)}$ (ng.h/mL)	C_{av} (ng/mL)
Diazepam	6469	269.5	7469	311.2	86.6%	86.6%
Nordiazepam	6334	263.9	8956	373.4	70.7%	70.7%

Based on published reports of elimination half-lives for diazepam and nordiazepam following multiple doses of diazepam (52.9 hours and 72 hours, respectively), steady state plasma concentrations of diazepam and nordiazepam would not theoretically be reached until approximately Day 14 [1, 2]. However, it was not considered possible, for ethical reasons, to increase the duration of diazepam treatment in volunteers. The results in the current study on Day 7 were consistent with achieving approximately 90% steady state plasma levels for diazepam and about 70% for nordiazepam at this time point. It was concluded that the differences in concentrations between Day 7 and 14 were accounted for by failure to be at steady state at Day 7 and not because of any interaction with acamprosate.

A comparison of $AUC_{(0-24)}$ values for acamprosate at Day 7 of Period B with values obtained at Day 14 of Period A showed no significant difference (*data not shown*).
One subject was dropped from participation on Day 13 of Period A because of edema and pain over the 5th right metatarsal. He was replaced. Otherwise, the study medications were well tolerated, with only minor adverse events.
Because diazepam may be used as a medication during alcohol withdrawal, it was of interest to administer it as monotherapy prior to concomitant therapy with acamprosate. It was concluded that there was no evidence of pharmacokinetic interaction of either diazepam and its metabolite (nordiazepam) or acamprosate when given in combination on multiple oral dosing.

AD 1135H (Decourt II) Research of Pharmacokinetic Interactions Between Imipramine and Acamprosate When Given in Combination on Multiple Oral Dosing

AD 1135H (Decourt II) was an open-label, randomized, 2 period, cross-over study of the pharmacokinetics of imipramine when given alone and when given in combination with acamprosate. It was conducted at [redacted] France from November 11, 1994 to December 23, 1994. The Principal Investigator was Dr. Jean-Philippe Decourt, MD, [redacted] Analytical work was performed by [redacted]
Sixteen healthy, adult male volunteers participated in the study. They ranged in age from 19 to 36 years (mean age: 24.1 years) and had body weights ranging from 58 to 86 kg (mean weight: 67.7 kg) and heights ranging from 158 to 186 cm (mean height: 175.0 cm). All 16 subjects completed both study periods.
The 2 study periods were as follows:
Period A: Two 333 mg tablets (666 mg) of acamprosate (Aotal®), three times daily (approximately, 8AM, noon, 8PM) from Days 1 to 10; and two 25 mg tablets of imipramine (Tofranil®) at 8 AM on Day 7.
Period B: Two 25 mg tablets of imipramine (Tofranil®) at 8 AM on Day 1.
Subjects were confined to the study site from Day -1 to Day 11 of Period A and from Day -1 to Day 3 of Period B. There was a 10 day washout period between the 2 study periods.
During Period A, blood samples were taken just prior to the first acamprosate dose on Day 1 and on Day 7, at the following time points: just prior to Dose 19 of acamprosate (time 0) and the dose of imipramine and then 0.5, 1, 1.5, 2, 3, 4 (just prior to Dose 20 of acamprosate), 5, 6, 8, 10, and 12 hours (just prior to Dose 21 of acamprosate). On Day 8, blood samples were taken at 18, 24 (just prior to Dose 22 of acamprosate), 28 and 36 hours. On Day 9, 48 hours (just before the 25th dose of acamprosate), and 60 hours. On Day 10 at 72 hours (just before the 28th dose of acamprosate) and on Day 11 at 96 hours.
During Period B, blood samples were taken just prior to the imipramine dose on Day 1(time 0) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours thereafter. On Day 2, samples were taken at 18, 24, 28 and 36 hours. On Day 3, samples were taken at 48 and 60 hours and on Day 4 at 72 hours and on Day 5 at 96 hours.
Imipramine and its main metabolite, desipramine, were assayed by a GC-MS method.
Mean (SD) values for pharmacokinetic parameters for imipramine and desipramine are shown below:

Pharmacokinetic Parameters of Imipramine after Administration of Imipramine with Acamprosate (Treatment A) or Alone (Treatment B)

Pharmacokinetic Parameter	Mean (SD) and [Minimum, Maximum] Values by Treatment Group		Statistical Analysis
	Treatment A (acamprosate and imipramine) (n = 16)	Treatment B (imipramine alone) (n = 16)	
C_{max} (ng/mL)	25.26 (8.30) —	25.54 (9.87) —	NS* (0.89-1.14)
T_{max} (h)	2.3 (1.0) —	2.4 (0.7) —	NS**
$t_{1/2}z$ (h)	12.6 (1.9) —	13.8 (3.2) —	P<0.05* (0.84-0.98)
AUC (ng.h/mL)	271.2 (96.0) —	299.3 (120.2) —	NS* (0.83-1.04)
MRT (h)	15.8 (2.2) —	17.3 (3.5) —	P<0.01 (0.87-0.96)

* = ANOVA (90% confidence interval around the ratio Treatment B/Treatment A)
** = Wilcoxon test

Pharmacokinetic Parameters of Desipramine after Administration of Imipramine with Acamprosate (Treatment A) or Alone (Treatment B)

Pharmacokinetic Parameter	Mean (SD) and [Minimum, Maximum] Values by Treatment Group		Statistical Analysis
	Treatment A (acamprosate and imipramine) (n = 16)	Treatment B (imipramine alone) (n = 16)	
C_{max} (ng/mL)	8.02 (2.32)	8.04 (2.75)	NS*
T_{max} (h)	3.6 (2.0)	7.1 (14.1)	NS**
$t_{1/2}z$ (h)	18.83 (3.41)	21.94 (8.11)	NS**†
AUC (ng.h/mL)	195.4 (74.7)	215.8 (105.9)	NS*†

* = 2-way ANOVA
** = Wilcoxon test
† = 15 subjects

The mean plasma imipramine and desipramine concentration-time profiles after administration of imipramine on Day 7 of multiple dosing with acamprosate (Treatment A) or after administration alone (Treatment B) were nearly superimposable. The 90% confidence intervals of the ratio of means were less than 0.8 to 1.2 for all parameters characteristic of imipramine bioavailability (C_{max}, AUC_t, MRT and $t_{1/2}z$).
There were no significant changes in safety laboratory parameters. There were some gastrointestinal side effects experienced by subjects, particularly during Treatment A on the day of acamprosate/imipramine coadministration, but these did not require specific treatment.

It was concluded that there was no significant difference in the pharmacokinetic patterns of either imipramine or its metabolite desipramine after single oral dosing of imipramine alone or when given on Day 7 of multiple oral dosing with acamprosate (666 mg tid).

ACAMP/US/97.1 (Dixon) was a double-blind, randomized, 3 period cross-over study of the pharmacokinetics and pharmacodynamics (cognitive function assessments) of acamprosate and naltrexone when multiple doses of these drugs were given separately and in combination. It was conducted at [ ] from Feb. 15, 1998 to April 6, 1998, with Russell M. Dixon, M.D. as Principal Investigator. Acamprosate measurement in biological samples was performed by [ ]

Twenty-five normal healthy adult volunteers (19 males and 6 females) were enrolled in the study and 24 completed their assigned treatment. Subject No. 22 was discontinued because of non-compliance after completion of the first treatment period and was replaced by Subject No. 122. Volunteers ranged in age from 21 to 40 years (mean age: 31.8 years), with body weights ranging from 60.8 to 88.5 kg (mean: 74.5 kg) and heights ranging from 157.0 to 189.0 cm (mean: 175.3 cm). All of the subjects were white, except for 1 Hispanic and 1 black subject.

Subjects were confined to the [ ] from Day-1 (the day prior to the first administration of study drug on Day 1) of each of the 3 study periods until completion of the last study procedure on Day 11. During each Treatment Period, pharmacokinetic blood samples were collected at baseline [i.e., on Day 1 prior to the first administration of study drug(s)], during the trough period on Days 5 and 6, and during the 96 hour PK profile period starting with the Day 7 dose. Pharmacodynamic (CNS Cognitive Function) testing and safety evaluations (including physical examination, neurological examination, clinical laboratory evaluations, vital signs, 12-lead ECGs) were monitored at screening, at check-in (Day -1) and/or at specified times during the study.

Subjects were randomly assigned to each of the following 3 treatments:

Treatment A: 1000 mg acamprosate (2x500 mg acamprosate enteric-coated tablets), administered orally q12h, starting at ±7AM for a total of 13 doses, plus 1 placebo capsule, administered orally q24h, starting at ±7AM for a total of 7 doses.

Treatment B: 2 placebo tablets (identical in appearance to acamprosate), administered orally q12h, starting at ±7AM for a total of 13 doses, plus a 50 mg over-encapsulated ReVia® (naltrexone) tablet, administered orally q24h, starting at ±7AM for a total of 7 doses.

Treatment C: 1000 mg acamprosate (2x500 mg acamprosate enteric-coated tablets), administered orally q12h, starting at ±7AM for a total of 13 doses, plus a 50 mg over-encapsulated ReVia® (naltrexone) tablet, administered orally q24h, starting at ±7AM for a total of 7 doses.

Blood samples for drug level measurement were obtained at the following time points during each of the 3 study periods: Day 1: prior to (within 5 minutes of) the first dose of study drug(s); trough levels on Days 5, 6, and 7; and at intervals up to 96 hours after the dose on Day 7.

Naltrexone and its major metabolite 6-β-naltrexol were assayed by a validated [ ] method by [ ]. Acamprosate was assayed by [ ] using a validated GC-MS method.

Pharmacokinetic parameters were calculated for naltrexone, 6-β-naltrexol, and acamprosate. Mean values for these parameters are shown in following tables:

Mean (SD) and Minimum, Maximum Values for Acamprosate Pharmacokinetic Parameters, Following Multiple Doses of Acamprosate Alone or with Naltrexone

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Acamprosate (Treatment A) (n = 24)		
C_{max} (ng/mL)	517 (183.6)	390 (160.0)	133	(118, 148)** (120, 156)†
AUC_{0-T} (ng.hr/mL)	4658 (1778.2)	3734 (1644.2)	125	(112, 137)** (114, 143)†
Kel (h^{-1})	0.054 (0.039)††	0.051 (0.026)‡	91.8	NA
$T_{1/2}$ (h)	17.9 (8.81) ††	18.5 (14.9) ‡	119	NA
T_{max} (h)	5.44 (3.08)	6.38 (2.87)	NA	NA

* = Test = Treatment C; Reference = Treatment A. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.
†† = n = 19
‡ = n = 20

Mean (SD) and Minimum, Maximum Values for Naltrexone Pharmacokinetic Parameters, Following Multiple Doses of Naltrexone Alone or with Acamprosate

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Naltrexone (Treatment B) (n = 24)		
C_{max} (ng/mL)	11.0 (4.76)	11.8 (6.55)	93.3	(79.6, 107)** (85.0, 109)†
AUC_{0-T} (ng.hr/mL)	38.0 (16.07)	38.6 (16.53)	98.4	(90.1, 107)** (92.0, 106)†
Kel (h^{-1})	0.225 (0.082)	0.223 (0.087)	101	NA
$T_{1/2}$ (h)	3.58 (1.62)	4.02 (3.49)	89.1	NA
T_{max} (h)	1.19 (0.46)	1.23 (0.33)	NA	NA

* = Test = Treatment C; Reference = Treatment B. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.

Mean (SD) and Minimum, Maximum Values for 6-β-Naltrexol Pharmacokinetic Parameters, Following Multiple Doses of Naltrexone Alone or with Acamprosate

Pharmacokinetic Parameter	Mean (SD) and [Minimum-Maximum] Values by Treatment Group		Percent Test/Reference*	90% Confidence Interval
	Naltrexone + Acamprosate (Treatment C) (n = 24)	Naltrexone (Treatment B) (n = 24)		
C_{max} (ng/mL)	91.3 (19.34)	96.1 (21.05)	95.0	(87.2, 103)** (88.1, 103)†
AUC_{0-T} (ng.hr/mL)	779 (128.3)	788 (134.8)	98.8	(95.0, 103)** (95.4, 103)†
Kel (h^{-1})	0.049 (0.013)	0.050 (0.012)	97.6	NA
$T_{1/2}$ (h)	15.1 (4.18)	14.7 (3.88)	103	NA
T_{max} (h)	1.25 (0.49)	1.21 (0.36)	NA	NA

* = Test = Treatment C; Reference = Treatment B. Ratio of untransformed parameter least square means expressed as a percentage.
** = 90% confidence interval for ratio of parameter least squares means of untransformed parameters.
† = 90% confidence interval for ratio of parameter least squares means of natural log transformed parameters.

There was a statistically significant pharmacokinetic interaction when acamprosate was administered twice a day in combination with a once daily administration of naltrexone for 7 days. Coadministration of naltrexone with acamprosate increased the rate and extent of absorption of acamprosate, as indicated by the 33% increase in acamprosate C_{max}, the 25% increase in the AUC_{0-T} and the shorter T_{max} values. Although these differences were statistically significant, they may not be clinically relevant. Naltrexone did not affect the elimination half-life of acamprosate. Acamprosate had no effects on the pharmacokinetic parameters of naltrexone or its major metabolite 6-β-naltrexol. Coadministration of the two drugs was well-tolerated by the subjects.

6.3 Renal study analysis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: **21-431**
Compound: Acamprosate Tablets
Sponsor: Lipha Pharmaceuticals
Type of Submission: 1P
Date of Submission: December 27, 2001
Reviewer: Sam H. Haidar, R.Ph., Ph.D.

Background:

This pharmacometric consult is for a renal impairment study which was included in the NDA submission, reviewed by Dr. David Lee (HFD-(870). Protocol summary and results are given below.

Study Summary

Study No.: AOTA-CIN IR1-AD 1003H

Study Title: Acamprosate pharmacokinetics study after single oral administration of two acamprosate tablets (2 x 333mg) to subjects with normal or impaired renal function

Objective: To evaluate the pharmacokinetics of acamprosate in healthy subjects and in patients with stable moderate to severe renal failure (creatinine clearance 30-60 and 5 – 29 mL/min) after the administration of a single dose of acamprosate.

Study Design: Open label, single dose, administered to 12 subjects with moderate or severe renal impairment and 6 normal subjects.

Blood Sampling and Analysis: Serial blood samples were collected at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours post administration of acamprosate

Pharmacokinetic Analysis: Non-compartmental analysis was performed by the sponsor. Table 1 lists the PK parameters for each group and the results of the statistical comparisons.

Table 1: **Mean values ± SEM**

	Group 1 Healthy subjects	Group 2 Cr.Cl. 30-60 ml/min	Group 3 Cr.Cl. 5-29 ml/min	Statistics
Cmax ($ng\ ml^{-1}$)	198±38	398±78	813±109	p<0.001 (1)
	NS	p<0.01		
	p<0.001			
Tmax (h)	5.83±1.33	4.33±0.76	23.33±7.67	p<0.05 (2)
	NS	p<0.05		
	p<0.05			
T½ (h)	18.21±3.21	33.35±6.58	46.62±12.85	p<0.05 (2)
	NS	NS		
	p<0.05			
MRT (h)	28.14±3.45	55.08±11.67	70.58±16.31	NS (2)
CL/F ($l\ h^{-1}$)	184.00±25.84	66.50±18.19	15.83±4.51	p<0.01 (2)
	p<0.01	p<0.01		
	p<0.01			
CL_R ($l\ h^{-1}$)	10.05±1.22	3.29±0.85	1.10±0.21	p<0.01 (2)
	p<0.01	p<0.05		
	p<0.01			
U %	5.57±0.79	4.26±0.63	6.19±0.76	NS (1)

(1) One Way ANOVA
(2) Kruskal-Wallis Test

Compartmental PK modeling was performed by the reviewer to explore dosage adjustment in renally impaired patients. Figure 1 shows the plasma concentration time profiles for each group. Figures 2 – 4 are the model predicted profiles and observed mean data for each group, while Figures 5 – 7 represent predicted steady state levels following multiple doses over 8 days.

Acamprosate PK after Single Dose (2 x 333 mg Tablets)

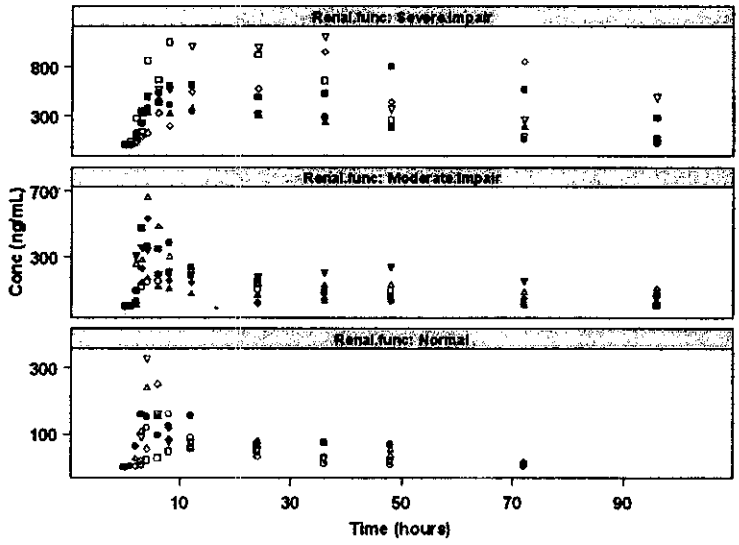


Figure 1.

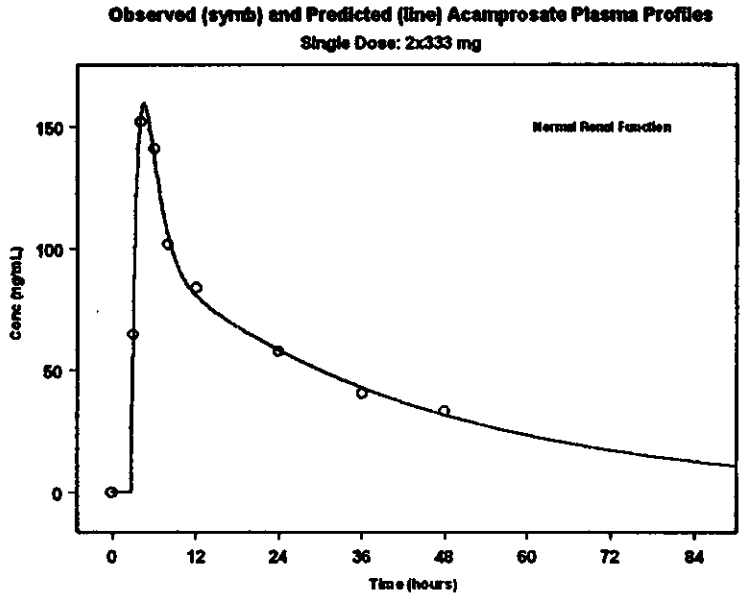


Figure 2.

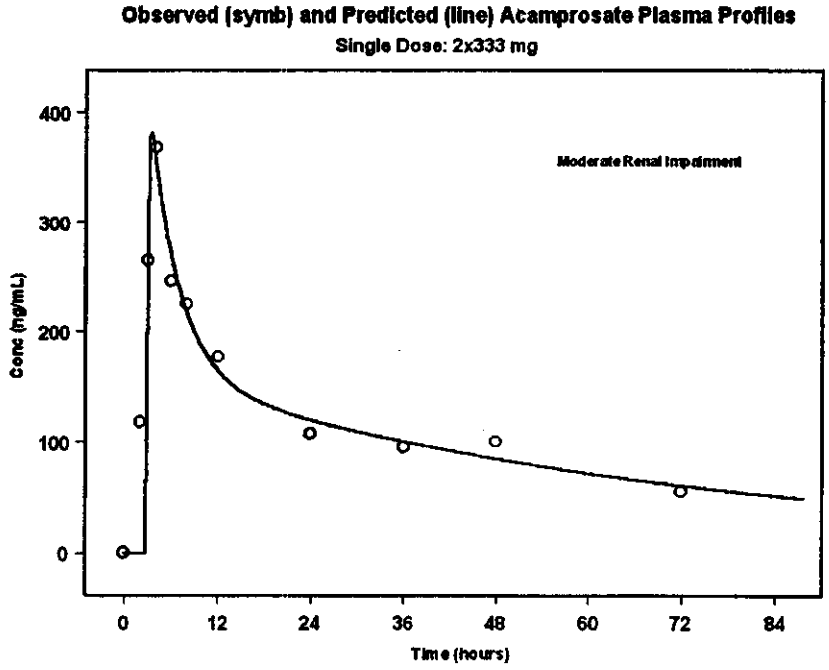


Figure 3.

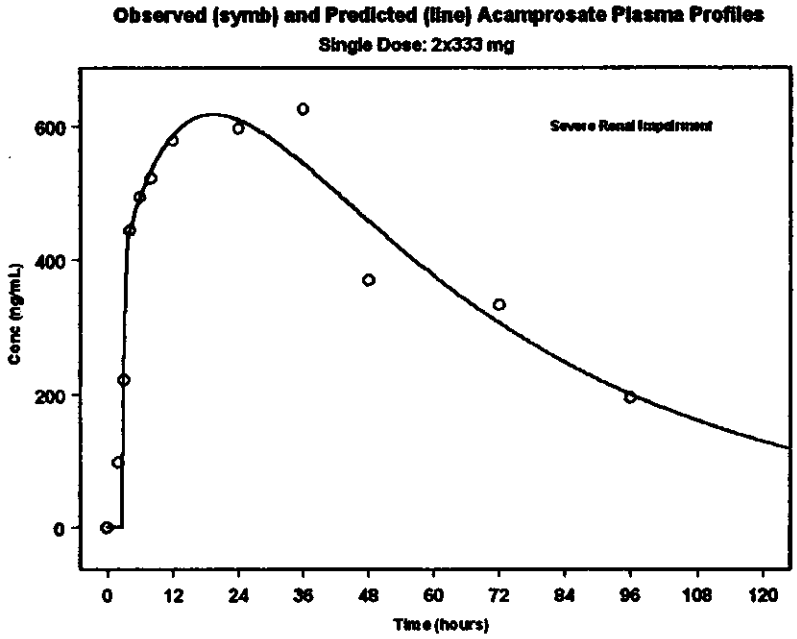


Figure 4.

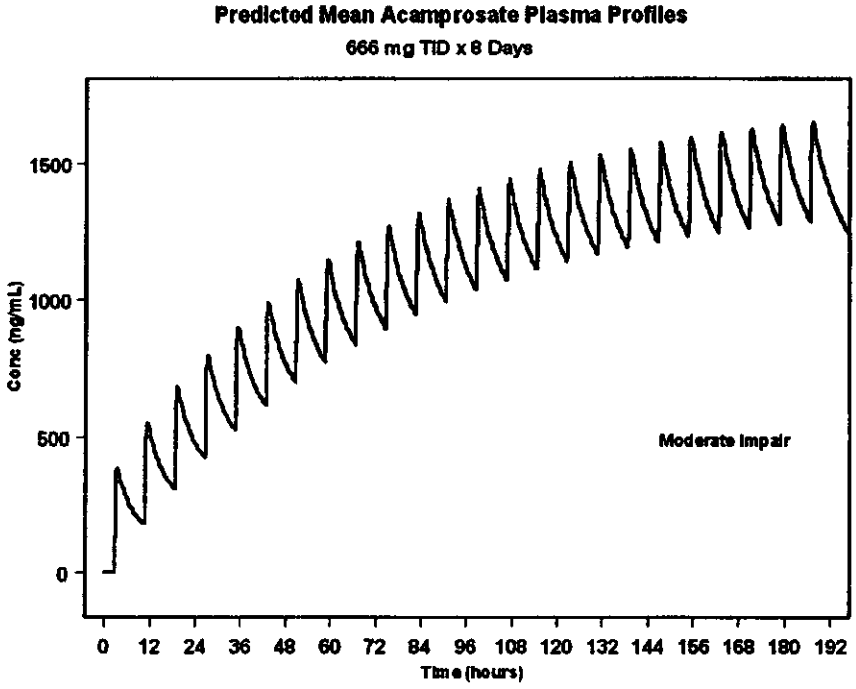


Figure 5

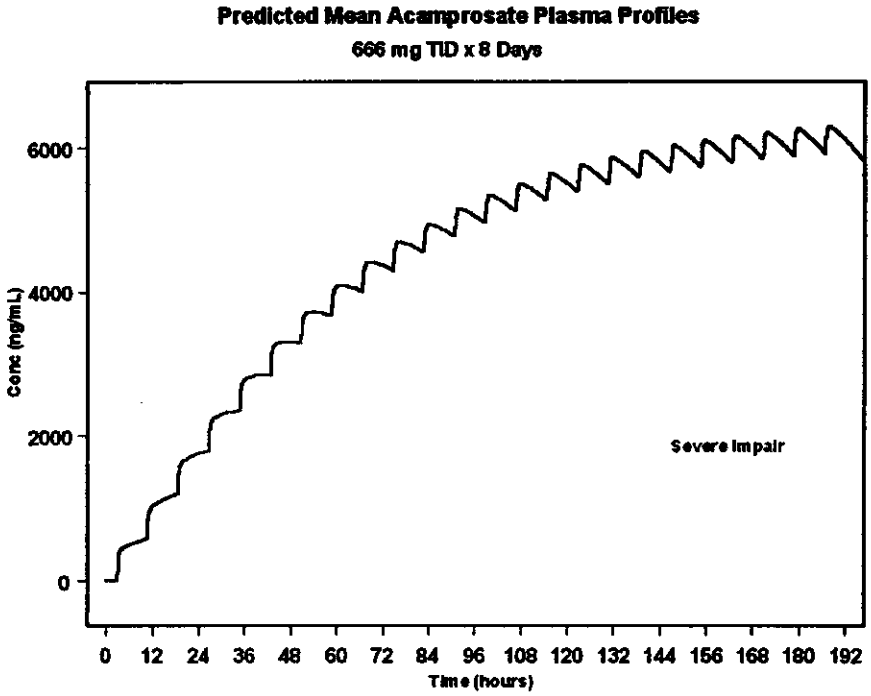

Predicted Mean Acamprosate Plasma Profiles
666 mg TID x 8 Days
Conc (ng/mL)
6000
4000
2000
0
Severe Impair
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Time (hours)

Figure 6

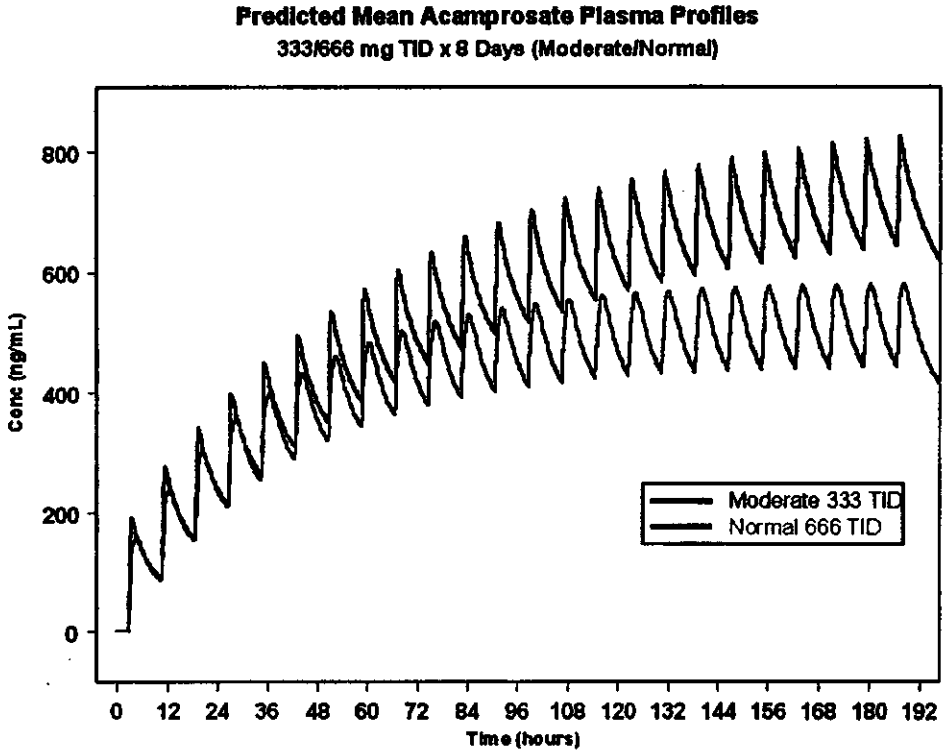


Figure 7

Reviewer Comments:

1. *Exposure was significantly higher in moderate and severe renal impairment compared to normal subjects.*
2. *Variability was high for all groups*
3. *Most patients in the severe renal impairment group had unpredictable profiles; therefore, it is recommended that acamprosate be contraindicated in this group, pending additional studies.*
4. *A dose of 333 mg TID is recommended for patients with moderate renal impairment. This dosing regimen would produce profiles/exposures which are closer to those produced in normal patients on the proposed dosing regimen of 666 mg TID.*

Sam H. Haidar, R.Ph., Ph.D.
Pharmacometrics
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

6.4 Additional dissolution information on acamprosate clinical lots used in BE and safety and efficacy studies

Bioequivalence studies

Dissolution data on Lots # 1519 and 1862, Initial and current formulations, respectively, used in 333 mg BE study: This is Method A

Study No.	Lot No.	Dosage strength	Formulation Designation	Date of test	Parameters of test [1]	Results		
						Individual values (% of calcium acamprosate dissolved)	Mean (%)	RSD (%)
AD993H, (*Fourtillan III*)	1519	333 mg	Initial formula	07/04/91	Method A 60 min 120 min[4]	 50.9, 47.9, 40.9, 43.2, 45.6, 45.3 74.5, 77.5, 80.3, 74.9, 82.4, 79.7	 45.6 78.2	 7.7 4.0
	1862	333 mg	Current formula	07/05/91	Method A 60 min. 120 min.[4]	 34.3, 39.0, 41.7, 42.8, 50.0, 47.5 65.0, 67.6, 76.4, 72.3, 83.6	 42.5 73.0	 13.3 10.1
		333 mg	Current formula	01/30/91	Method A 60 min. 90 min.	 43.9, 39.9, 45.2, 39.3, 42.7, 45.5 62.4, 64.7, 71.2, 65.0, 64.5, 64.9	 42.7 65.5	 6.2 4.5
AD1044H, (*Fourtillan V*)	1519	333 mg	Initial formula	07/04/91	Method A 60 min 120 min[4]	 50.9, 47.9, 40.9, 43.2, 45.6, 45.3 74.5, 77.5, 80.3, 74.9, 82.4, 79.7	 45.6 78.2	 7.7 4.0
	1862	333 mg	Current formula	07/05/91	Method A 60 min. 120 min.[4]	 34.3, 39.0, 41.7, 42.8, 50.0, 47.5 65.0, 67.6, 76.4, 72.3, 83.6	 42.5 73.0	 13.3 10.1
		333 mg	Current formula	01/30/91	Method A 60 min. 90 min.	 43.9, 39.9, 45.2, 39.3, 42.7, 45.5 62.4, 64.7, 71.2, 65.0, 64.5, 64.9	 42.7 65.5	 6.2 4.5

Comparison of acamprosate 666 mg three times daily vs. 500 mg two times daily tablets

Dissolution on Lots # 0264 (333 mg) and # 3432 (500 mg) for 666 mg three times daily vs. 500 mg two times daily (Theodor I study).

Study No.	Lot No.	Dosage strength	Formulation Designation	Date of test	Parameters of test [1]	Results		
						Individual values (% of calcium acamprosate dissolved)	Mean (%)	RSD (%)
SS401 (*Theodor I*)	0264	333 mg	Initial formula	06/23/99	Method B 90 min 120 min.	 101.3, 86.5, 97.5, 91.1, 101.3, 90.2 102.6, 89.0, 98.6, 91.0, 102.3, 91.1	 94.6 95.8	 6,3 6.1
	3432	500 mg	Current formula	05/06/99	Method B 90 min 120 min.	 90.0, 87.6, 87.7, 82.4, 82.3, 89.2 99.9, 99.0, 100.7, 97.7, 97.5, 102.1	 86.5 99.5	 3.9 1.6

European Efficacy and Safety Trials dissolution data

Paille Efficacy and Safety Study used # 41319, 41328, 41368

Study No.	Lot No.	Dosage strength	Formulation Design ation	Date of test	Parameters of test [1]	Results		
						Individual values (% of calcium acamprosate dissolved)	Mean (%)	RSD (%)
544 (Paille)	41319	333 mg	Initial formula	-	-	Not available[2]	-	-
	41328	333 mg	Initial formula	-	-	Not available[2]	-	-
	41368	333 mg	Initial formula	-	-	Not available[2]	-	-

Note: #2 No dissolution data are available on these lots since no dissolution test was required for release of tablets but only a disintegration test , according to European Pharmacopoeia specifications.

Pelc II Efficacy and Safety Study used # 1624

Study No.	Lot No.	Dosage strength	Formulation Design ation	Date of test	Parameters of test [1]	Results		
						Individual values (% of calcium acamprosate dissolved)	Mean (%)	RSD (%)
AD 10 089 (*Lesch*)	1624	333 mg	Initial formula	-	-	Not available[2]	-	-
AOTA/LP 90/N001 (*UKMAS*)	1624	333 mg	Initial formula	-	-	Not available[2]	-	-

Note: #2 No dissolution data are available on these lots since no dissolution test was required for release of tablets but only a disintegration test , according to European Pharmacopoeia specifications.

PRAMA Efficacy and Safety Study used # 3251

No dissolution data available.

ACAMP/US/96.1 Study

This study used two lots, # 3556 and # 3570. Dissolution information on lots # 3556 and 3570 were obtained from the following studies:

Study No.	Lot No.	Dosage strength	Formulation Design ation	Date of test	Parameters of test[1]	Results		
						Individual values (% of calcium acamprosate dissolved)	Mean (%)	RSD (%)
ACAMP/ US/97.1, (*Dixon*)	**3556**	500 mg	Current formula	03/07/97	Method B 90 min.	**67.1, 70.4, 67.7, 67.5, 69.8, 70.4**	**68.8**	2.3
ACAMP/ F/97.1 (*ADES*)	0200	333 mg	Initial formula	-	-	Not available[2]	-	-
	3570	500 mg	Current formula	04/11/97	Method B 90 min. 120 min.	**88.4, 96.1, 76.6, 76.9, 78.3, 97,4 98.2, 99.8, 88.6, 89.4, 91.2, 99.6**	**85.6 94.5**	-

It is interesting to note that Lot # 3556 mean % dissolved is considerably low compared with that of the Lot # 3570 mean % dissolved. At this time, the consequences of this discrepancy are unknown to this reviewer. The % differences in dissolution may have some clinical implications.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lee
6/7/02 03:50:17 PM
BIOPHARMACEUTICS

Sam H. Haidar
6/7/02 04:02:00 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/10/02 07:25:03 AM
BIOPHARMACEUTICS