

CLINICAL PHARMACOLOGY STUDIES ¹¹										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ¹²	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
89027, (Weber) W. Weber, Germany	C (March 22, 1989 to April 7, 1989)	Volume 39	NR, SC, OL, 3 sequential period comparative PK study: Period 1: SnD solution; Period 2: SnD tablet; Period 3: MD X 6 days, with SnD on Day 7. Washout phase of ≥7 days between Periods 1 & 2. Period 3 begins 24 hrs after Period 2 dosing. (9 days)	Period 1: Acamp, powder for oral sol'n, 666 mg (#1882)	666	SnD solution, fasting	6, HV (6)	24-45 (34.2)	6/0 (100/0)	ND
			Period 2: Acamp, tabs, 333 mg (#1519)	666	SnD, fasting					
			Period 3: Acamp, tabs, 333 mg (#1519)	1332	4 tabs/day (ii-i-i) X 6 days, ii tabs on D7					

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
RD 298/17163 (Dewland I) P.M. Dewland, United King.	C (Dec. 20, 1988 to Feb. 28, 1989)	Volume 40	R, SC, DB, PC, 2 Group, MuD rising dose safety & PD (psycho-motor effects) study. Each group (A, B) of 9 subjects (6 active, 3 placebo) participated for 2 non-consecutive study periods. 2 week washout between periods. (14 days)	Acamp, tabs, 333 mg (#1962) Placebo, tabs (#1963)	Group A <i>Period 1</i> Active 666 1332 <i>Placebo</i> 2-4 tabs <i>Period 2</i> Active 1998 3996 <i>Placebo</i> 6-12 tabs	Group A <i>Period 1</i> Active 2 tabs, SnD, Days 1 & 7 2 tabs bid, Days 2-6 <i>Placebo</i> 2 tabs, SnD, Days 1 & 7 2 tabs bid, Days 2-6 <i>Period 2</i> Active 6 tabs, SnD, Days 1 & 7 6 tabs bid, Days 2-6 <i>Placebo</i> 6 tabs, SnD, Days 1 & 7 6 tabs bid, Days 2-6	19, HV (18) ¹⁶ 9, HV (9) 6 (6) 3 (3) 6 (6) 3 (3)	19-44 (28.1)	19/0 (100/0)	ND

¹⁶ Nineteen subjects in total in the study (Group A: 6 active, 3 placebo; Group B: 7 active, 3 placebo), because one subject in Group B dropped out during the second treatment period and was replaced.

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
RD 298/17163 (Dewland I) P.M. Dewland, United King. (cont'd)					Group B <i>Period 1</i> <i>Active</i> 1332 2664 <i>Placebo</i> 4-8 tabs	Group B <i>Period 1</i> <i>Active</i> 4 tabs, SnD, Days 1 & 7 4 tabs bid, Days 2-6 <i>Placebo</i> 4 tabs, SnD, Days 1 & 7 4 tabs bid, Days 2-6	10, HV (9) 6 (6) 3 (3)			
					<i>Period 2</i> <i>Active</i> 2664 5328 <i>Placebo</i> 8-16 tabs	<i>Period 2</i> <i>Active</i> 8 tabs, SnD, Days 1 & 7 8 tabs bid, Days 2-6 <i>Placebo</i> 8 tabs, SnD, Days 1 & 7 8 tabs bid, Days 2-6	7 (6) 3 (3)			
RD 298/17927 (Dewland II) P.M. Dewland, United King.	C (March 13, 1990 to April 13, 1990)	Volume 41	NR, SC, SB, 4-part SnD rising dose PK study of acamp. oral solutions. 7 day washout between doses. (4 days)	Acamp, oral solution, 333 mg powder (#3011); 1332 mg (#3011)	333 666 1332 2664	SnD sol'n, fasting SnD sol'n, fasting SnD sol'n, fasting SnD sol'n, fasting	6 HV (6) 6 (6) 6 (6) 6 (6)	26-36 (29.5)	6/0 (100/0)	ND

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
SS409 (Theodor II) R.A. Theodor, Germany	C (Oct. 25, 1994 to Dec. 19, 1994)	Volume 42	R (within group), SC, DB, PC, 4- sequential group, multiple dose (8 days), rising dose PK study of acamp. oral solutions. Different subject group at each dose level. 14 day interval between start of next group.	Treatment A ¹⁷ Acamp., aqueous sol'n, 300 mg/10 mL (#3458)	Treat. A: 600 mg	(All groups) 10 mL of respective dose q12h for 8 days.	Treat. A: 12 HV (12)	Treat. A: 18-40 (27.9)	Treat. A: 15/0 (100/0)	Treat. A: 15/0/0/0 (100/0/0/0)
				Treatment B: Acamp., aqueous sol'n, 500 mg/10 mL (#3465)	Treat. B: 1000 mg		Treat. B: 12 HV (12)	Treat. B: 18-39 (26.5)	Treat. B: 15/0 (100/0)	Treat. B: 15/0/0/0 (100/0/0/0)
				Treatment C: Acamp., aqueous sol'n, 800 mg/10 mL (#3460)	Treat. C: 1600 mg		Treat. C: 13 HV (12)	Treat. C: 19-40 (27.2)	Treat. C: 17/0 (100/0)	Treat. C: 17/0/0/0 (100/0/0/0)
				Treatment D: Acamp., aqueous sol'n, 1000 mg/ 10 mL (#3461)	Treat. D: 2000 mg		Treat. D: 13 HV (12)	Treat. D: 20-37 (29.7)	Treat. D: 15/0 (100/0)	Treat. D: 15/0/0/0 (100/0/0/0)
				Placebo, aqueous sol'n (#3457)	Placebo: 20 mL		Placebo 12 HV (12)			

¹⁷ Within each of the 4 treatment groups (A-D), each of which had 15 volunteers, 12 were randomly assigned to active drug and 3 to placebo.

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Meram: Feb. 6, 1991 ¹⁸ (Jaillon) P. Jaillon, France	C (1988- 89)	Volume 43	R, SC, DB, SnD, PC, 4-way XO study of IV Acamp. PK & tolerance at 3 active dose levels (10, 20, and 30 mg/kg) vs placebo (all SnD). Blood and urine samples for 24 hours post-dose. 7-day washout between periods. (3 days)	Acamp, inj. Sol'n 5g/100 ml (ND)	10 mg/kg: 710.83 ± 52.82	IV (pump) over 10 min, (fasting)	12, HV (12)	18-28 (23)	12/0 (100/0)	ND
			Acamp, inj. Sol'n 5g/100 ml (ND)	20 mg/kg: 1421.67 ±105.64	IV (pump) over 10 min, (fasting)					
			Acamp, inj. Sol'n 5g/100 ml (ND)	30 mg/kg: 2132.50 ±158.47	IV (pump) over 10 min, (fasting)					
			0.9% NaCl inj. sol'n	0.9% NaCl inj. sol'n	IV (pump) over 10 min, (fasting)					

¹⁸ Study does not have an official number (Meram study) and is thus identified by date of study report.

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AD875H, (<i>Fourtillan II</i>) JB Fourtillan, France	C (Oct. 10, 1989 to Aug. 27, 1990)	Volumes 43-44	OL, SC, 3 sequential period comparative PK study: Period 1=SnD Acamp; Period 2=MD Acamp.X 7 days; Period 3 = IV SnD Acamp. Washout of ≥14 days between Periods 1 & 2; ≥17 days between Periods 2 & 3. (9 days)	Period 1: Acamp, tabs, 333 mg (#1519)	666	SnD	24, HV (24)	20-35 (27)	24/0 (100/0)	ND
				Period 2: Acamp, tabs, 333 mg (#1519)	1998	1 tab tid X 7 days	24 HV (24)			
				Period 3: Acamp, injectable, 1 g/10 ml (#0428)	666	SnD, IV infusion over 15 minutes	24 HV (24)			
Bioequivalence/Bioavailability										
AD864H, (<i>Fourtillan I</i>) J.B. Fourtillan, France	C (June 7, 1989 to July 17, 1989)	Volume 45	R, SC, OL, 2-period XO PK study of SnD acamp tab vs acamp solution. Washout of ≥7 days between periods. (2 days)	Acamp, tabs, 333 mg (#1519)	666	SnD, fasting	6, HV (6)	21-34 (27)	6/0 (100/0)	ND
				Acamp, sachet, 666 mg/sachet (#1882)	666 in 100 ml water	SnD, fasting				

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AD993H, (<i>Fourtillan III</i>) J.B. Fourtillan, France	C (Sept. 2, 1991 to Oct. 11, 1991)	Volume 45	R, SC, OL, 2-period XO PK study of SnD acamp, comparing 2 different formulations. Treatment A = reference formulation; Treatment B = new formulation. Washout of ≥ 7 days between periods. (2 days)	<i>Treatment A:</i> Acamp, tabs, 333 (#1519)	666	<i>Treatment A:</i> SnD with 150 ml water (fasting)	12, HV (12)	19-30 (24.7)	12/0 (100/0)	ND
				<i>Treatment B:</i> Acamp, tabs, 333 (#1862)	666	<i>Treatment B:</i> SnD with 150 ml water (fasting)	12 HV (12)			
AD1044H, (<i>Fourtillan V</i>) J.B. Fourtillan, France	C (July 16, 1992 to Sept. 26, 1992)	Volume 46	R, SC, OL, 2-period XO PK study of MD acamp, comparing 2 different formulations. Treatment A = reference formulation; Treatment B = new formulation. Washout of ≥ 14 days between periods. (16 days)	<i>Treatment A:</i> Acamp, tabs, 333 (#1519)	1998	<i>Treatment A:</i> 2 tabs tid X 8 days	16, HV (16)	18-33 (24.2)	16/0 (100/0)	ND
				<i>Treatment B:</i> Acamp, tabs, 333 (#1862)	1998	<i>Treatment B:</i> 2 tabs tid X 8 days	16 HV (16)			
SS401 (<i>Theodor I</i>) R.A. Theodor, Germany	C (Aug. 8, 1994 to Oct. 9, 1995)	Volume 47	R, SC, OL, 2-way XO PK study (Day 1 and at steady state) of MD acamp, given according to 2 different schedules (Treatments A and B). Each treatment period lasted 9 days, without washout. (18 days)	<i>Treatment A:</i> Acamp, tabs, 333 mg (#0264)	1998	<i>Treatment A:</i> 2 tabs tid X 9 days	24 HV (24)	18-40 (28.5)	24/0 (100/0)	ND
				<i>Treatment B:</i> Acamp, tabs, 500 mg (#3432)	2000	<i>Treatment B:</i> 2 tabs q 12h X 9 days	24 HV (24)			

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Pharmacokinetic: Effects of Food										
AD1011H, (<i>Fourtillan IV</i>) JB Fourtillan, France	C (Oct. 21, 1991 to Nov. 17, 1991)	Volume 50	R, SC, OL, 2-way XO study of SnD Acamp tabs in fasting (Treatment A) vs non-fasting (Treatment B) condition, to assess food effect on PK. Washout ≥ 7 days between periods. (2 days)	Treatment A: Acamp, tabs, 333 mg (#3250) Treatment B: Acamp, tabs, 333 mg (#3250)	666 666	SnD with 150 ml water (fasting) SnD with 150 ml water (after standard meal)	12, HV (12) 12, HV (12)	20-31 (24.8)	12/0 (100/0)	ND
Pharmacokinetic: Male vs Female and Special Populations										
RD 298/20673 (<i>Dewland IV</i>) P.M. Dewland, United King.	C (Jan. 17, 1994 to March 28, 1994)	Volume 50	NR, SC, OL, SnD comparison of acamprostate PK in males and females. (1 day)	Acamp, tabs, 333 mg (#0233)	666	SnD (fasting)	24, HV (24)	21-46 (31)	12/12 50/50	ND
AOTA-CIN PA1-AD 1054H (<i>Pelc III</i>), I. Pelc, Belgium	C (Feb. 24, 1992 to Dec. 7, 1992)	Volume 51	NR, SC, OL, MD acamp PK in ADS, post-alcohol withdrawal (≥ 5 days). PK comparison with HV from study AD 875H. (28 days)	Acamp, tabs, 333 mg (#3250)	1998	2 tabs tid X 28 days	9, ADS	30-62 (41.9)	7/2 (78/22)	ND

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AOTA-CIN IR1-AD 1003H, (Sennesael) J. Sennesael, Belgium	C (Feb., 1991 to Aug., 1991)	Volume 51	OL, SC, SnD acamp PK comparison of moderate RI (CrCl 30-60 ml/min) vs severe RI (CrCl <30 ml/min) vs HV. (1 day)	Acamp, tabs, 333 mg (#1519)	666	SnD with 150 ml water (fasting)	6 mod. RI (6) 6 sev. RI (6) 6 HV (6)	36-67 (56.8) 34-69 (51.2) 22-39 (29.3)	3/3 (50/50) 6/0 (100/0) 6/0 (100/0)	ND
AOTA-CIN IHP1, (Miguet) JP Miguet, France	C (1990)	Volume 52	OL, SC, SnD pilot PK in HI (1 day)	Acamp, powder, 666 mg/sachet (#3011)	666	SnD oral solution (fasting)	6 HI (6)	34-70 (56.5)	5/1 (83/17)	ND
90235, (Haug) G. Haug, Germany	C (May, 1991)	Volume 52	OL, SC, MD PK in mild HI (Child- Pugh Grade A) vs mod. HI (Child-Pugh Grade B) vs HV. (8 days)	Acamp, tabs, 333 mg (#1519)	1998	2 tabs tid X 7days; Day 8, SnD.	6 mild HI (6) 6 mod. HI (6) 6 HV (6)	37-62 (52.5) 44-56 (50.8) 46-54 (50.5)	4/2 (66/33) 6/0 (100/0) 5/1 (83/17)	ND

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Pharmacokinetic: Drug Interactions										
12/89-03 AL, (Lücker) P.W. Lücker, Germany	C (April 24, 1989 to May 20, 1989)	Volume 53	R, SC, SB (subject), PC, MD, 2-way XO (acamp vs placebo) study of acamp effects on ethanol PK. 7-day washout between periods. (3 days)	Acamp, tabs, 333 mg (#1243) + 40% ethanol on Day 3	1998 32 g	2 tabs tid X 2 days; Day 3, SnD (fasting), with ethanol 2 hrs post- final dose	12 HV (12)	22-34 (26.0)	12/0 (100/0)	12/0/0/0 (100/0/0/0)
				Placebo, tabs, (#1242) + 40% ethanol on Day 3	6 tabs 32 g	2 tabs tid X 2 days; Day 3, SnD (fasting), with ethanol 2 hrs post- final dose	12 HV (12)			
RD 298/17949, (Dewland III) P.M. Dewland, United King.	C (April 25, 1990 to May 22, 1990)	Volume 54	R, SC, OL, SnD, 2 period XO PK study (acamp with or without alcohol). Washout ≥7 days between periods. (2 days)	Acamp, tabs, 333 mg (#3249) co- dosed with 40% ethanol in orange juice	1332 0.9 g/kg LBW q 30 min for 7.5 hrs	SnD + ethanol in orange juice; then, ethanol q 30 min. over 7.5 hrs.	12 HV (12)	19-38 (24.5)	12/0 (100/0)	ND
				Acamp, tabs, 333 mg (#3249) co- dosed with orange juice	1332	SnD + orange juice; then orange juice q30 min.	12 HV (12)			

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
RD 298/20828, (Dewland V) P.M. Dewland, United King.	C (Sept. 12, 1994 to Nov. 23, 1994)	Volumes 54-55	R, SC, OL, MD, 2 period XO (Treatment 1: acamp Days 1-14, with disulfiram on Days 8-14; Treatment 2: disulfiram, Days 1-7). Washout of ≥14 days between treatment periods. (14 days)	Acamp, tabs, 333 mg (# 1402) Esperal® (disulfiram), tabs, 500 mg (# SWP 60)	1998 500	<i>Treatment 1:</i> 2 acamp tabs tid X 14 days + disulfiram, 1 tab/day, Days 8-14. <i>Treatment 2:</i> Disulfiram, 1 tab/day for 7 days	20 HV (20) 20 HV (20)	20-41 (31)	20/0 (100/0)	ND
AD1126H, (Decourt I) J-P Decourt, France	C (May 1, 1994 to Aug. 21, 1994)	Volume 56	R, SC, OL, MD, 2-period XO study (Period A: diazepam without [Days 1- 7] or with [Days 8 to 14] acamp; Period B: acamp alone [Days 1-7]). Comparison of acamp and diazepam PK when each drug was given alone vs when given in combination (Day 7 and 14 of Period A, Day 7 of Period B). Washout of 10 days between Periods A and B. (14 days)	Acamp, tabs, 333 mg, #41614/0251 Valium® (diazepam), tabs, 5 mg (#F002X)	1998 10	<i>Period A:</i> Diazepam, 1 tab q12h from Day 1 to 14; Acamp, 2 tabs tid from Day 8 to 14. <i>Period B:</i> Acamp, 2 tabs tid from Day 1 to 7.	17 HV (16) 17 HV (16)	18-30 (23.6)	17/0 (100/0)	ND

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
AD1135H, (Decourt II) J-P Decourt, France	C (Oct. 31, 1994 to Dec. 23, 1994)	Volumes 56-57	R, SC, OL, MD (acamp) and SnD (imipramine), 2-period XO study (Period A: acamp Day 1-10, with SnD imipramine on Day 7; Period B: SnD imipramine). Comparison of imipramine PK, with or without acamp. Washout of 10 days between Periods A and B. (10 days)	Acamp, tabs, 333 mg (#0273) Tofranil® (imipramine), tabs, 25 mg (#1014)	1998 50	<i>Period A:</i> Acamp, 2 tabs tid from Day 1 to 10. Imipramine, 1 tabs (SnD) on Day 7. <i>Period B:</i> Imipramine, 2 tabs (SnD).	16 HV (16) 16 HV (16)	19-36 (24.1)	16/0 (100/0)	ND
ACAMP/US/ 97.1, (US 97.1) R. Dixon, USA	C (Feb. 15, 1998 to April 6, 1998)	Volumes 58-61	R, SC, DB, MD, 3-period XO study (Treatment A: acamp and naltrexone for 7 days; Treatment B: placebo for acamp and naltrexone for 7 days; Treatment C: acamp and placebo for naltrexone for 7 days), comparing acamp and naltrexone PK and cognitive function tests, alone and in combination. Washout of 7 days between each period. (14 days)	Acamp, tabs, 500 mg (#3556) Placebo for acamp (#3557) ReVia® (naltrexone), overencapsul- ated tabs, 50 mg (#3639) Placebo for naltrexone, capsule (#3638)	1000 4 tabs 50 1 cap	<i>Treatment A:</i> Acamp, 2 tabs q12h X 13 doses + placebo for naltrexone, 1 cap daily X 7. <i>Treatment B:</i> Placebo for acamp, 2 tabs q12h X 13 doses + naltrexone, 1 cap daily X 7. <i>Treatment C:</i> Acamp, 2 tabs q12h X 13 doses + naltrexone, 1 cap daily X 7.	25 HV (24) 24 HV (24) 24 HV (24)	21-40 (31.8)	19/6 (76/24)	23/1/1/- (92/4/4/-)

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Pharmacodynamic: CNS Effects										
Meram, Oct. 16, 1986, (Poenaru) S. Poenaru, France	C (?1986)	Volume 207	NR, SC, OL, MD, 4 sequential period interaction study; acamp/ethanol effects on sleep physiology: Period 1= reference; Period 2=SnD ethanol; Period 3=acamprostate for 14 d; Period 4=acamp and SnD ethanol (15 days)	Acamp, tabs, 333 mg (ND)	1332	4 tabs/d (ii-i- i) X 15 days	14 HV (14)	20-49 (28)	7/7 (50/50)	ND
				Ethanol, 40%	0.30 ml/kg	SnD X 2 (alone and after 15 days of acamp)	14 HV (14)			
AFB 06/0081- 89 (Hermann) WM Hermann, Germany	C (1989)	Volumes 208-209	R, SC, DB, PC, AC, 4-period XO study of SnD acamp (2 dose levels) vs diazepam vs placebo on EEG and psychometric tests. 7-day washout between periods (2 days)	Acamp, OE caps, 200 mg (#1824)	400	SnD	20 HV (16) 17 HV (16)	20-38 (27.4)	20/0 (100/0)	ND
				Acamp, OE caps, 200 mg (#1824)	800	SnD	18 HV (16)			
				Diazepam, OE caps, 10 mg (#11017)	10	SnD	17 HV (16)			
				Placebo caps (#331 K2258356)	--	SnD	17 HV (16)			

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				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
Oct. 19, 1987 (Moser I) L. Moser, Germany	C (1987)	Volume 210	R, SC, DB, PC, AC, 3-period XO study of SnD acamp vs diazepam (Valium®) vs placebo on psychometric tests relevant to driving. 7-day washout between periods. (1 day)	Acamp, OE caps, 333 mg (#1629)	666	SnD	18 HV (17)	22-43 (28.2)	9/9 (50/50)	ND
				Diazepam (Valium®), OE caps, 10 mg (#7656) + 1 placebo	10 + 1 plac. caps	SnD	17 HV (17)			
				Placebo caps	2 caps	SnD	18 HV (17)			
Nov. 6, 1987 (Moser II) L. Moser, Germany	C (9/28, 1987 to 10/15, 1987)	Volume 210	R, SC, DB, PC, AC, 3-period XO study of SnD acamp + ethanol vs diazepam (+placebo) + ethanol vs placebo + ethanol on psychometric tests relevant to driving. 7-day washout between periods. (1 day)	Acamp, OE caps, 333 mg (1629) + ethanol, 40%	666	2 caps, SnD	24 HV (24)	22-43 (29.1)	24/0 (100/0)	ND
				Diazepam, OE caps, 10 mg + placebo caps + ethanol, 40%	10	1 caps, SnD + 1 caps SnD	24 HV (24)			
				Placebo caps + ethanol, 40%	2 caps 0.75g/kg	2 caps, SnD SnD	24 HV (24)			

CLINICAL PHARMACOLOGY STUDIES ¹¹										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ¹²	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
ACAMP/F/95.1 (Macher I) J.P. Macher, France	C (Oct. 16, 1995 to Jan. 26, 1996)	Volume 211	R, SC, DB, PC, 2-way XO study of SnD IV acamp vs IV placebo on cerebral magnetic resonance spectroscopy. ≥7 days to <2 month washout between periods. (1 day)	Acamp, radio- labeled (¹³ C), IV solution, 150 mg/10 ml (#3497). Placebo = sterile 0.9% NaCl solution (#3496).	15 mg/kg (max. = 1500 mg) Compar- able volume	SnD IV infusion over 15 minutes with auto. Infusion device. SnD IV infusion over 15 minutes with auto. Infusion device.	8 HV (8) 8 HV (8)	20-39 (27.75)	8/0 (100/0)	ND

CLINICAL PHARMACOLOGY STUDIES ¹¹										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ¹²	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed) ¹³	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
ACAMP/F/96.1 (Macher II) J.P. Macher France (cont'd)						<i>Treatment 3:</i> Placebo for acamp, 2 tabs tid with meals X 9 days + placebo for nal, 1/day X 9 days. SnD ethanol ingested over 15-20 min on Days 8 and 9 (one dose per day).	20 HV (20)			
Pharmacodynamic: Other										
AOTA/S/91.1 (Borg) S. Borg, Sweden	C (Dec., 1991 to Nov., 1993)	Volume 215	Pro, SC, R, DB, PC, PG (2: acamp vs placebo) in ADS, motivated to become abstinent, post-withdrawal from alcohol. Study of biological markers of alcohol consumption vs self-reports. (26 weeks)	Acamp, tabs, 333 mg (#3306) Placebo, tabs (#3305)	1998 6 tabs	2 tabs tid 2 tabs tid	7ADS (5) 7 ADS (5)	ND (44.2) ¹⁹ ND (47.6)	5/0 (100/0) 5/0 (100/0)	ND ND

¹⁹ Values are based only on the 5 patients in each treatment group who completed all visits.

10.5.3 Group III Studies: Early Clinical Experience Studies in the Revised ISS

EARLY CLINICAL EXPERIENCE: CONTROLLED AND UNCONTROLLED CLINICAL TRIALS ²⁰										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ²¹	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
-- (Hillemand I) B. Hillemand, France	C (March 1, 1982 to Oct. 31, 1983)	Volume 216	Pro, SC, R, DB, PC, PG (2: acamp vs P), in ADS subjects, post-alcohol withdrawal, with dosing based on body weight (see Total Daily Dose). All patients also received meprobamate (400-800 mg/day) and B1 and B6 vitamins. (90 days)	Acamp, caps., 250 mg (#3656)	25 mg/ kg (≥1500 and ≤2500 mg/day)	ND	42 ADS (20)	25-58 (43.2)	33/9 (79/21)	ND
				Placebo, caps (ND)	6-10 caps/day (1 cap/ 10 kg)	ND	43 ADS (16)	22-52 (40.4)	39/4 (91/9)	ND

²⁰ The following abbreviations will be used throughout:

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

²¹ Dates are given as M/D/Y, when available.

EARLY CLINICAL EXPERIENCE: CONTROLLED AND UNCONTROLLED CLINICAL TRIALS ²⁰										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ²¹	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
-- (Hillemand II) B. Hillemand, France	C (1988)	Volume 216	Pro, SC, NR, OL study of acamp in ADS, post-alcohol withdrawal. Patients also received meprobamate (800-1200 mg/day for 30 days) and B1 and B6 vitamins. (90 days)	Acamp, caps., 250 mg (batch number: ND)	750	1 caps tid	11 ADS (4)	30-55 (42.1)	9/2 (82/18)	ND
-- (Poinso) Y. Poinso, France	C (1986)	Volume 216	Pro, SC, R, OL, PG (3: acamp, 750 mg/day vs acamp 1000 mg/day vs acamp 1500 mg/day) study in ADS, post-alcohol withdrawal. (90 days)	Acamp, caps, 250 mg (batch number: ND)	Group 1: 750 Group 2: 1000 Group 3: 1500	Group 1: 1 caps tid Group 2: 2 caps bid Group 3: 2 caps tid	Group 1: 10 ADS (3) Group 2: 10 ADS (7) Group 3: 10 ADS (6)	Group 1: 33-52 (42.9) Group 2: 28-63 (45.3) Group 3: 31-58 (43.9)	Group 1: 10/0 (100/0) Group 2: 8/2 (80/20) Group 3: 8/2 (80/20)	ND ND ND

EARLY CLINICAL EXPERIENCE: CONTROLLED AND UNCONTROLLED CLINICAL TRIALS ²⁰										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ²¹	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Enrolled per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
-- (Lhuître) J.P. Lhuître, France	C (Nov, 1984 to June, 1986)	Volumes 216-219	Pro, MC, R, DB, PC, PG (2: acamp vs P), in ADS subjects, post-alcohol withdrawal. (90 days)	Acamp, tabs, 333 mg (Meram #001)	1332	2-1-1 tabs tid	279 ADS (175)	ND (42.6)	228/51 (82/18)	ND
				Placebo, tabs (ND)	4 tabs	2-1-1 tabs tid	290 ADS (181)	ND (42.4)	238/52 (82/18)	ND
AA 11 087, (Pelc I) I. Pelc, Belgium	C (Jan., 1988 to Feb., 1990)	Volume 220	Pro, MC, R, DB, PC, PG (2: acamp vs P), with pre-randomization stratification according to body weight, in ADS, post-alcohol withdrawal. (180 days)	Acamp, tabs, 333 mg (#1243 and 1375)	1998* (1332)	2 tabs tid	55 ADS (24)	ND (42.2)	37/18 (67/33)	ND
				Placebo, tabs (#1242)	6 tabs (4 tabs)	2-1-1 tabs tid				
-- (Roussaux) J.P. Roussaux, Belgium	C (1987 to 1989)	Volume 220	Pro, SC, R, DB, PG (2: acamp vs P), with pre-randomization stratification according to body weight, in ADS, post-alcohol withdrawal. (90 days)	Acamp, tabs, 333 mg (batch number: ND)	1998* ²² (1332)	2 tabs tid	63 ADS (44)	ND (42.7)	49/14 (78/22)	ND
				Placebo, tabs	6 tabs (4 tabs)	2 tabs bid				

²² In studies marked with an asterisk (*), daily dosage for patients in these studies was on the basis of body weight. For patients with a bodyweight greater than 60 kg: 2 tabs of acamprosate (666 mg) or placebo three times daily (total daily acamprosate dose of 1998 mg). For patients with a bodyweight less than 60 kg: 2 tabs of acamprosate (or placebo) in the morning, 1 tab at midday and 1 tab in the evening for Pelc I; 2 tabs of acamprosate (666 mg) or placebo twice daily for Roussaux (total daily acamprosate dose of 1332 mg).

10.5.4 Group IV Studies: Phase IV Open-Label Clinical Trials in the Revised ISS

TABULAR SUMMARY OF GROUP IV STUDIES: UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ²³										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ²⁴	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
PHASE IV STUDIES (COMPLETED)										
Jan. 8, 1991 (<i>MERAM Phase IV</i>) B. Granger, France	C (ND) ²⁵	Volume 221	Pro, MC, NR, OL uncontrolled Ph IV study of acamp in ADS, post- withdrawal from alcohol. (90 days)	Acamp, tabs, 333 mg (Batch number: ND)	1332	2-1-1 tabs tid, preferably before meals	860 ADS (663)	20-81 (42.6)	671/187 (78/22)	ND

²³ The following abbreviations will be used throughout:

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

²⁴ Dates are given as M/D/Y, when available.

²⁵ No information is available on when study was conducted. Report is dated, Jan. 8, 1991.

TABULAR SUMMARY OF GROUP IV STUDIES: UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ²⁵												
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ²⁴	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics				
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)		
AOTA/F/91.6 (ASATIM) ²⁶ D. Barrucand, France	C (Dec. 1, 1991 to June 24, 1992)	Volumes 221-222	Pro, MC, NR, OL study in ADS undergoing inpatient alcohol withdrawal. PG (4: Group A ²⁷ : acamp and Atrium®; Group B: acamp and Equanil®; Group C: acamp and Seresta®; and Group D: acamp alone). (15 days)	Acamp, tabs, 333 mg (#3250 and 3306)	Grp. A: Acamp, 1998 + Atrium, 300	Grp. A: Acamp, 2 tabs tid + Atrium, either 300 mg o.d. or 100 mg tid	Grp. A: 201 ADS (184)	Grp. A: ND (40.5)	Grp. A: 170/31 (85/15)	ND		
				Atrium®, tabs, 300 or 100 mg								
				Equanil®, tabs or injectable, 250 mg tab or unit dose	Grp. B: Acamp, 1998 + Equanil, 500	Grp. B: Acamp, 2 tabs tid + Equanil, 1 tab or 1 IM injection bid	Grp. B: 139 ADS (130)	Grp. B: ND (42.0)	Grp. B: 114/25 (82/18)	ND		
				Seresta®, tabs, 10 mg	Grp. C: Acamp, 1998 + Seresta, 20	Grp. C: Acamp, 2 tabs tid + Seresta, 1 tab bid	Grp. C: 123 ADS (105)	Grp. C: ND (40.8)	Grp. C: 101/22 (82/18)	ND		
				Grp. D: Acamp, 1998	Grp. D: Acamp, 2 tabs tid	Grp. D: 128 ADS (117)	Grp. D: ND (38.7)	Grp. D: 106/22 (83/17)	ND			

²⁶ AOTA/F/91.6 (ASATIM), although presented in this table, is summarized in Section 8.3.6.1 of the original NDA.

²⁷ Atrium® = febarbamate (150 mg), difebarbamate (105 mg) and phenobarbital (14 mg); Equanil® = meprobamate (250 mg); Seresta® = oxazepam (10 mg). Minimum daily doses of these drugs were as follows: Atrium, 300 mg; Equanil, 500 mg; Seresta, 20 mg.

TABULAR SUMMARY OF GROUP IV STUDIES: UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ²³										
Study #, (Common Name) Principal Investigator, Country	Status (Start – End Dates) ²⁴	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
CAMP/B/95.1 (NEAT: Belgium) I. Pelc, Belgium	C (May, 1995 to Nov., 1996)	Volumes 223-224	Pro, MC, NR, OL study of acamp (dosage according to body weight) ²⁸ in ADS, motivated to become abstinent, who were assigned to one of 5 psychosocial treatment groups ^{**29} . (24 weeks).	Acamp, tabs, 333 mg (#0002, 0003, 0004 and 0007)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	614 ADS (226)	ND (42.9)	413/201 (67/33)	ND
CAMP/B/95.1 Extension (NEAT: Belgium-Ext.) I. Pelc, Belgium	C (May, 1995 to June, 1997)	Volume 225	Pro, MC, NR, OL study of continued acamp treatment for ADS completing all visits of CAMP/B/95.1. (24 weeks)	Acamp, tabs, 333 mg (#0002, 0003, 0004 and 0007)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	147 ADS (87)	ND (45)	89/58 (61/39)	ND

²⁸ For studies where acamprosate dose is marked with an asterisk (*), daily dosage was on the basis of body weight. For patients with a bodyweight greater than 60 kg: 2 tabs of acamprosate (666 mg) in the morning, 2 tabs of acamprosate (666 mg) in the afternoon, and 2 tabs of acamprosate (666 mg) in the evening (*total daily dose of 1998 mg*). For patients with a bodyweight less than 60 kg: 2 tabs of acamprosate (666 mg) in the morning, 1 tab of acamprosate (333 mg) in the afternoon, and 1 tab of acamprosate (333 mg) in the evening (*total daily dose of 1332 mg*). Doses were to be taken between meals.

²⁹ In studies marked with a double asterisk (**), the non-randomly assigned psycho-social therapy could be either: 1) group therapy; 2) individual psychotherapy; 3) relapse prevention/coping strategies; 4) brief intervention; or 5) family therapy. In CAMP/GB/95.1, family therapy was not offered.

TABULAR SUMMARY OF GROUP IV STUDIES: UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ²³										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ²⁴	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
CAMP/CH/ 95.1 (NEAT: Switzerland) W. J. Fuchs, Switzerland	C (Nov., 1995 to Jan., 1997)	Volumes 226-227	Pro, MC, NR, OL study of acamp (dosage according to body weight) in ADS starting alcohol detoxification and motivated to abstinence, who were assigned to one of 5 psychosocial treatment groups**. (24 weeks).	Acamp, tabs, 333 mg (#0003 and 0004)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	105 ADS (62)	ND (44.2)	80/25 (76/24)	ND
CAMP/A/95.1 (NEAT: Austria) F. Fischer, Austria	C (Jan., 1996 to Jan., 1997)	Volumes 227-228	Pro, MC, NR, OL study of acamp (dosage according to body weight) in ADS who were assigned to one of 5 psycho-social treatment groups**. (24 weeks).	Acamp, tabs, 333 mg (#0002)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	111 ADS (69)	ND (42.6)	100/11 (90/10)	ND
CAMP/GB/ 95.1 (NEAT:UK) M. Morgan, United King.	C (Nov., 1995 to Dec., 1996)	Volumes 229-230	Pro, MC, NR, OL study of acamp (dosage according to body weight) in ADS motivated to become abstinent, who were assigned to one of 4 psychosocial treatment groups**. (24 weeks).	Acamp, tabs, 333 mg (#0002, 0003, 0004 and 0007)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	225 ADS (46)	ND (43.9)	179/46 (80/20)	ND
CAMP/P/95.1 (NEAT: Portugal) A.J.P. Preto, Portugal	C (Aug. 19, 1996 to Dec. 31, 1997)	Volumes 231-232	Pro, MC, NR, OL study of acamp (dosage according to body weight) in ADS starting alcohol detoxification and motivated to abstinence, who were assigned to one of 5 psychosocial treatment groups**. (24 weeks).	Acamp, tabs, 333 mg (#0004)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	234 ADS (143)	ND (41.0)	216/18 (92/8)	ND

TABULAR SUMMARY OF GROUP IV STUDIES: UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS ²³										
Study #, (Common Name) Principal Investigator, Country	Status (Start - End Dates) ²⁴	Volume Location of Study Report in Original NDA	Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
				Drug, Dosage Form, Strength (Formulation & Batch #)	Total Daily Dose in mg	Regimen	#, Type of Patients Entered per Group (# completed)	Age Range (mean)	Sex: M/F (%)	Race: W/B/H/O (%)
ACAMP/D/ 96.1 (INTEGRAL) M. Soyka, Germany	C (May 2, 1996 to Sept. 29, 1997)	Volumes 232-233	Pro, MC, NR, OL study of acamp (dosage according to body weight) in ADS starting alcohol detoxification and motivated to abstinence, who were assigned to one of 5 psychosocial treatment groups**. (24 weeks).	Acamp, tabs, 333 mg (#0007, 0021 and 0064)	1998* (1332)	2 tabs tid 2-1-1 tabs tid	753 ADS (359)	ND (43.8)	544/209 (72/28)	ND
ACAMP/F/97.1 (ADES) J. Ades, France	C (April, 1997 to Oct., 1997)	Volumes 233-234	Pro, MC, R, OL, PG (2: acamp, 1000 mg bid vs acamp, 666 mg tid) study in ADS motivated be withdrawn from alcohol. Study compared dosage schedules. (2 months)	Acamp, tabs, 333 mg (#0200) Acamp, tabs, 500 mg (#3570)	1998 2000	2 tabs tid, with meals 2 tabs bid, at breakfast and with evening meal	65 ADS (48) 68 ADS (55)	ND (42.8) ND (42.1)	52/13 (80/20) 56/12 (82/18)	ND ND

NDA No. 431
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I concur with Dr. Winchell's conclusions and recommendations

1ST CYCLE CLINICAL
REVIEW

**NDA 21-431
Acamprosate**

**Clinical Efficacy Review and
Overall Executive Summary**

**Celia Jaffe Winchell, M.D.
Medical Team Leader, Addiction Drug Products
Division of Anesthetic, Critical Care, and Addiction Drug Products
June 7, 2002**

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- 10.2.7 AD 10 089 (Lesch): Double-Blind Controlled Study versus Placebo to Assess the Effectiveness and Tolerance of AOTA-Ca in Treatment Which Helps to Maintain Abstinence after Detoxification in the Alcoholic Patient 152
- 10.2.8 AOTA/P/89.1 (Barrias): A Study of the Efficacy and Safety of AOTA-Ca to Maintain Abstinence in the Weaned Alcoholic Patient. A Double-Blind Comparison Versus Placebo 156
- 10.2.9 AA.11.088 (Besson): A Clinical Study to Assess the Efficacy and Tolerance of Acamprosate in Maintaining Abstinence in the Weaned Alcoholic Patient during the Detoxification Period. A Double-blind Study Versus Placebo 160

Clinical Review of NDA 21-431

Executive Summary

1 Recommendations

1.1 Recommendation on Approvability

Acamprosate has been demonstrated to be superior to placebo in maintaining abstinence from alcohol in recently-detoxified alcoholics. The effect, though modest in longer-term studies, is significant whether one compares the number of subjects surviving without relapse to the end of the study, or the number of on-study visits at which subjects are assessed by the investigator as abstinent. However, the evaluation of acamprosate's safety profile has been complicated by inconsistencies in the safety database.

Based on the clinical efficacy data, the application is approvable. However, resubmission of the safety datasets with clarification of the inconsistencies is required to facilitate review of the safety profile. Because it is not yet clear whether the safety profile is acceptable, non-approval is recommended.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

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

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

2 Summary of Clinical Findings

Acamprosate, a homotaurine derivative with modified polarity, was synthesized in order to improve the cerebral transfer of homotaurine. Homotaurine (3-amino-propanesulfonic acid) is a higher homologue of the naturally occurring amino acid, taurine, with structural similarities to the neurotransmitter, γ -amino butyric acid (GABA). Acamprosate appears to restore balance between the inhibitory transmitter GABA and the excitatory transmitter glutamate, with a major mechanism being the normalization of function of glutamate receptors of the NMDA receptor subtype, thus playing a role in the treatment of alcoholism. Acamprosate is marketed in 39 countries. It was first made available in France in 1989, and Lipha estimates that over 1 million patients with alcohol dependence have been treated with acamprosate since that time.

2.1 Brief Overview of Clinical Program

Product Name: Acamprosate (calcium acetylamino propane sulfonate)

Route Of Administration: Oral

Indication: []

This application contained three pivotal trials, one lasting three months and two lasting roughly a year. In addition, safety data and summaries of efficacy results were provided for 9 additional 6-month studies and 3 one-year studies. Full safety and efficacy datasets were also provided for the single U.S. study in the clinical program. In all but the U.S. study, the indication studied was the maintenance of abstinence in alcoholics who had completed a formal detoxification program. The U.S. study enrolled individuals who had not been detoxified and sought to evaluate acamprosate's role in promoting abstinence; it was not a successful trial.

The pivotal trials included 375 placebo-treated subjects, 372 subjects treated with the dose regimen of acamprosate now proposed for marketing, and 251 treated with a lower daily dose of acamprosate. The quantitation of overall safety exposure is complicated by the varying methods of adverse event ascertainment in the different trials. Only 5 studies (the U.S. study, the two one-year pivotal efficacy studies, and two other 6-month non-pivotal European studies) collected spontaneously reported adverse events. All other studies used a checklist and did not routinely record events that were not on the checklist.

2.2 Efficacy

In three European pivotal efficacy studies, subjects randomized to acamprosate were more likely than subjects randomized to placebo to be assessed by the clinician as abstinent, using either continuous abstinence or intermittent periods of abstinence as the success measure. These measures of efficacy differ from the sponsor's labeling claim, which reports the [] The method of ascertainment of the number of drinking days in the European studies was insufficiently systematic to allow for precise counting of number of days drinking or not drinking. Therefore, although the data support the claim that acamprosate is effective in maintaining abstinence in recently-detoxified alcoholics, it is not possible to quantify the effect in terms of specific duration of abstinence. The single U.S. study failed to support the efficacy of acamprosate, and this discrepancy was addressed in a meeting of the Psychopharmacologic Drugs Advisory Committee on May 10, 2002. The recommendation of the Committee was to accept the validity of the European studies (pending inspection), and to regard the American study as a failure, providing neither evidence of *lack* of efficacy, nor evidence of efficacy in any particular subgroup. The constrained setting in which evidence of efficacy has been demonstrated in European studies (i.e., only in patients who had completed an inpatient detox) was noted.

The three trials which provided evidence of efficacy were:

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

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

The results of the complete abstinence analysis are shown in the table below for the three pivotal trials. For Pelc-II, the values listed here are the proportions of subjects listed as having a “Time to first relapse” of >90 days. (Statistical Report Table 5.6, vol 76, page 30). For Paille, the values listed are the proportions of subjects listed as having a time of continuous abstinence of at least 360 days. The additional 6 months of off-treatment follow-up are not considered here. For PRAMA, the values listed are the numbers of subjects coded as not relapsing in the uncensored analysis (i.e. dropout is considered relapse). Note that, although the acamprosate subjects are all presented under the 1998 mg/day column, dosing in this study was 1998 mg/day for subjects >60 kg and 1332 mg/day for lighter subjects. Only 24 subjects assigned to acamprosate received the 1332 dose.

Study	Duration of treatment	Treatment		
		Placebo	Acamprosate 1332 mg/day	Acamprosate 1998 mg/day
Pelc-II	90 days	9/62 (15%)	26/63 (41%)	26/63 (41%)*
Paille	360 days	20 (11%)	34 (18%)	33 (19%)**
PRAMA	48 weeks (336 days)	16 (12%)	N/A	39 (29%) ***

*p<.0009, chi-square

**P<.05, chi-square comparison of 1998 mg/day vs. placebo, if dropouts are considered relapses. If dropouts are censored, p=0.11

***p=.0004, chi-square, if dropouts are considered relapses. If dropouts are censored, p=.051

As shown above, the statistical significance of the results depends on assumptions made about dropouts. Considering all dropouts to have relapsed is a common approach in

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addiction treatment trials, because the likelihood of dropout is greatly increased by relapse to drug use. However, this is likely to be an overestimate of the relapse rate in dropouts. Because each trial had more dropouts in the placebo arm than in the active treatment arm(s), this analysis introduces some bias toward finding a difference in favor of the drug. However, consistent results on other analyses (e.g. time to first relapse, number of visits at which subjects were assessed as abstinent) provides some reassurance. Additional support is provided by several additional studies (of 6 months to 1 year), conducted in various countries, which were submitted without primary datasets for review, but which report statistically significant results on the continuous abstinence measure.

Although the number of subjects considered successful by definition used in the complete abstinence analysis is small (less than 20% in the Paille study), the clinical significance of success as defined in this manner in the longer studies is unquestionable.

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

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

Inspection of one site participating in the Paille trial and one site participating in the PRAMA trial revealed no concern about fraud. However, some "sloppiness" was observed, such as a subject being classified as abstinent despite elevated blood alcohol levels recorded in the CRF, and a subject being classified as non-abstinent due to "missing data" which was, in fact, present in the CRF. Such findings further underscore the need to consider the efficacy data from the European studies cautiously.

2.3 Safety

The review of safety data was performed by Drs. Michael J. Sevka and Charles Cooper. Because of inconsistencies in coding and in flagging of serious adverse events, discrepancies in the numbers of deaths reported, and other problems with the data, few firm conclusions can be drawn. It is difficult to summarize with confidence even the number of exposed patients and duration, adequacy of monitoring and follow-up, as studies varied considerably in the methods of ascertainment of safety findings. Only three studies of approximately 6 months (US 96.1, UKMAS, and ADISA) and two studies of approximately one year

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(PRAMA and Paille) fully captured spontaneously-reported adverse events. These studies enrolled 1275 subjects randomized to acamprosate (1062 at the proposed recommended dose or higher).

All other studies used a 43-item checklist for collection of adverse events and any AE not included on the list was recorded as "other." If the event led to discontinuation, it was included on the CRF and was captured in a retrospective review of CRFs. Therefore, most serious AEs for these studies are also captured.

The table below illustrates the different assessments collected in various Phase 3 studies. Not reflected in the table is the variability in the specific laboratory assessments performed, their timing and extent. However, the table does illustrate the difficulty in establishing appropriate groupings for safety analysis.

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Table 2.3: Enrollment and Assessments in Phase 3 Studies

Common Name	Total Patients	Daily Acamprosate Dose			Placebo	Study Duration (actual exposure varied greatly)	Adverse Events		Vital Signs ²	Laboratory Assessments ³	ECG ⁴
		1332 mg	1998/2000 mg	3000 mg			Spontaneously Reported	Reported by Checklist ¹			
Double-Blind, Placebo-Controlled Short-Term Studies											
US 96.1	601		258	83	260	6 months (24 weeks)	X		X	X	X
Pelc II	188	63	63		62	90 days (13 weeks)		X ⁴	X	X	
Poldrugo	246	31*	91*		124	180 days (26 weeks)		X ⁴	X	X	
Tempesta	330		164		166	180 days (26 weeks)		X ⁴		X	
UKMAS	581		289		292	24 weeks	X		X	X	X
BENELUX	262	32*	96*		134	180 days (26 weeks)		X	X	X	
ADISA	295		147		148	180 days	X		X	X	
Ladewig	61	9*	20*		32	180 days (26 weeks)		X ⁴		X	
Total in short-term studies capturing spontaneous adverse events		0	694	83	700						
Total in studies measuring ECGs			547	83	552						

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Common Name	Total Patients	Daily Acamprosate Dose				Study Duration (actual exposure varied greatly)	Adverse Events		Vital Signs ²	Laboratory Assessments ³	ECG ⁴
		1332 mg	1998/2000 mg	3000 mg	Placebo		Spontaneously Reported	Reported by Checklist ¹			
Double-Blind, Placebo-Controlled Long-Term Studies											
PRAMA	272	24*	112*		136		X		X	X	
Paille	538	188	173		177		X		X	X	
Lesch	448	34*	190*		224			X	X	X	
Barrias	302	48*	102*		152			X ⁴	X	X	
Besson	110	11*	44*		55			X ⁴	X	X	
Total in long-term studies capturing spontaneous adverse events		212	285		313						
Total in all studies capturing adverse events		212	979	83	1013						

* Dosing based on body weight (≤ 60 kg or >60 kg). Patients with a body weight ≤ 60 kg who were randomized to the acamprosate group received 1332 mg acamprosate daily. Patients with a body weight >60 kg who were randomized to the acamprosate group received 1998 mg acamprosate daily.

¹ The checklist consisted of a 43-item questionnaire.

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

³ Specific laboratory values assessed varied by study. Very few studies, for example, measured coagulation parameters.

Studies with baseline and postbaseline ECG data.

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

Note: Total Patients is based on the Safety Population.

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It is not clear whether deaths and SAEs are also captured for Phase 1 and 2 studies, or for the extensive Phase 4 European studies.

Because overall group N's cannot be determined with confidence for the various groupings of reports, no rates can be calculated to compare the incidence of serious side effects to the rates in the placebo groups.

In general, the most common side effect that appears to be clearly drug-related within individual studies (where N's can be readily ascertained) is diarrhea. Reports of pruritis and transient hypotension are also notable in literature.

The safety testing in the development program appears to have given little attention to evaluating cardiac conduction effects of acamprosate. Only two clinical trials recorded ECG's at any point during treatment. Cardiac effects may require additional evaluation if data are not available from earlier studies.

The overall safety database is large, but as noted, the ascertainment of safety findings was inconsistent and, by current standards, incomplete. Furthermore, subjects over age 65 were routinely excluded from most studies. Polysubstance abusers were not included in most studies, but are prevalent in the target population in the U.S. Few women were included. Renal impairment was also grounds for exclusion in most trials. Safety issues in these subpopulations may arise after marketing.

2.4 Dosing

The dosing regimen recommended in the proposed labeling is 333 mg, two tablets t.i.d. Lower doses were studied in earlier development, but only one positive study supporting a regimen of 1332 mg/day was submitted with data in support of this application. This study, Pelc-II, was brief (3 months), and a longer (1 year) study of this regimen, Paille, did not demonstrate efficacy for the lower-dose regimen. A dose-response relationship is not clear, as the Pelc-II study had identical results for both dose groups. Dose toxicity relationships may be difficult to evaluate, as much of the safety database employed dosing based on weight, assigning the lower dose only to smaller subjects.

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

2.5 Special Populations

Overall, women, the elderly, and minorities were poorly represented in the clinical trials database. Only 129/2287 subjects in the integrated safety database were over age 60; even fewer were over 65 as most studies excluded such subjects per protocol. Information about race was collected only in the single U.S. study. Therefore, analysis of effects of race on efficacy cannot be conducted (as the trial was not successful) and analysis of effects of race on safety are limited.

There do not appear to be gender differences in effectiveness. Safety analysis (based on sponsor's summaries, and therefore subject to revision when safety data is resubmitted) by gender shows few treatment-by-gender interactions in favor of placebo. The exception is diarrhea, which seemed to be more prevalent in the female subjects on acamprosate (27%, vs 20% in males) while the rates in placebo groups (~12%) were similar across genders.

Subjects over 65 were excluded from the European studies per protocol (although some appear to have been included). Only 6% of subjects (129/2287) in the integrated safety database were ≥ 60 years old. Therefore, exposure in this demographic group was small and may represent an area for further exploration. The older subjects showed trends toward greater treatment group difference (in favor of placebo) in the rates of adverse events reported in several body systems (based on sponsor's summaries, and therefore subject to revision when safety data is resubmitted).

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

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

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

CLINICAL REVIEW

1 INTRODUCTION AND BACKGROUND

1.1 General Information

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

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

1.2 State of Armamentarium for Indication

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

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

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

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

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

1.3 Important Milestones in Product Development

Acamprosate is a synthetic molecule, originally identified by Laboratoires Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. Acamprosate was authorized for marketing in France, for the indication of maintaining abstinence from alcohol post-withdrawal, in 1987 and has been commercially available (as Aotal) there since 1989, in the 333 mg tablet strength. Lipha also markets the acamprosate 333 mg tablets (as Campral) in 38 additional countries. On 6/25/96, Lipha met with the agency in a Pre-IND meeting to discuss plans to seek marketing authorization in the United States. The initial program proposed consisted of a single multi-center efficacy trial using a new (but compositionally proportional) 500 mg tablet, intended to offer a simpler (b.i.d.) regimen with a total daily dose very similar to the labeled dose for the 333 mg tablet (2000 mg as 500 mg, ii p.o. b.i.d. vs 1998 mg as 333 mg ii p.o. t.i.d.). The single U.S. trial was to support the application as a pivotal safety and efficacy trial; two completed European trials using the 333 mg tablet were to be submitted as confirmatory evidence of efficacy. When the U.S. trial failed to demonstrate superiority of acamprosate over placebo, further discussions were held and Lipha elected to submit an application for the 333 mg tablet using the European data as pivotal.

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

6/25/96	Pre-IND meeting	Proposal to study 500 mg tablet (ii p.o. b.i.d) in a single U.S. study, and to submit this plus two completed European studies of 333 mg tablet (ii p.o. t.i.d.) as pivotal. Agreement in principle by Agency.
10/29/96	IND 51,809 opened	
10/27/98	"update" meeting	Need for safety data in polysubstance abusers discussed; sponsor also encouraged to consider geriatric and pediatric issues.
1/27/00	Pre-NDA meeting	US Trial failed to meet primary efficacy endpoint; post-hoc analysis proposed but not accepted by Agency. Plan for NDA revised to current approach of seeking marketing authorization for 333 mg tablet using completed European trials as support.
6/7/00		Letter from NIAAA indicating that there were no concerns about the applicability of European data to the American alcoholic population.
12/27/01	NDA submission	
5/1/02	PDAC Meeting	Discussion of conflicting results of American vs. European studies

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1.4 Other Relevant Information

1.4.1 Foreign Marketing Status

Acamprosate is marketed in 39 countries. It was first made available in France in 1989, and Lipha estimates that over 1 million patients with alcohol dependence have been treated with acamprosate since that time. The table below (sponsor's in-text table 3.3.1) illustrates acamprosate's global regulatory status as of 11/01.

Table 1.4.1 Foreign Marketing Status of Acamprosate

Country	Regulatory Authority	Date of Approval	Date of Marketing	Manufacturer	Formulation	Strength	Quantity	Expiration Date
ARGENTINA	National	19.09.1996	13.05.1997	MERCK QUIMICA ARGENTINA	Compend	46200	60, 84, 180, 200	01.04.2000
AUSTRALIA	National	30.10.1997	08.1999	LIPHA SA	Compend	-	-	10.1999
AUSTRIA	National	20.09.1994	23.04.1996	MERCK GmbH WIEN	Compend	1 - 21427	84*	01.07.1996
	National (2nd application)	09.06.1997	22.01.1998	LIPHA S.A. LYON	Acamprosate "LIPHA"	1-22348	84, 168	
BELGIUM	EU multi-state	18.11.1994	29.08.1996	MERCK BELGOLABO	Compend	177 IS 14 F 3	24, 84*	21.04.1997
BOLIVIA	National	14.08.1995	23.03.1999	INTIBOLIVIA	Compend	18-19424/99	84	-
BRAZIL	National	25.03.1998	06.10.1998	MERCK BRAZIL	Compend	790	48, 84	01.04.2000
CHILE	National	02.09.1996	30.09.1997	MERCK QUIMICA CHILENA	Compend	P-0024197	10, 12, 20, 24, 30, 36, 48, 50, 60, 72, 84*	13.06.1998
COLOMBIA	National	08.11.1996	03.11.1997	MERCK COLOMBIA S.A.	Compend	M-007271	84	-
COSTA RICA	National	04.1998	16.01.1999	MERCK CENTROAMERICAN A	Compend	-	84	-
CZECH REPUBLIC	National	01.08.1996	23.11.1998	LIPHA SA LYON	Compend	17/32996-C	60, 84, 200	01.01.2000
DENMARK	National	12.01.1995	05.11.1999	LIPHA SA LYON	Compend	17543	-	03.2000
DOMINICAN REPUBLIC	National	04.2000	21.06.2001	MERCK CENTROAMERICAN A	Subsid	2001-1047	84	
ECUADOR	National	10.11.97	01.12.1998	MERCK ECADOR	Compend	22490-11-01	84	-

1.5 Important Issues with Pharmacologically Related Agents

There are no pharmacologically related agents.

2 CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

Much of the material below is taken from the sponsor's NDA summary.

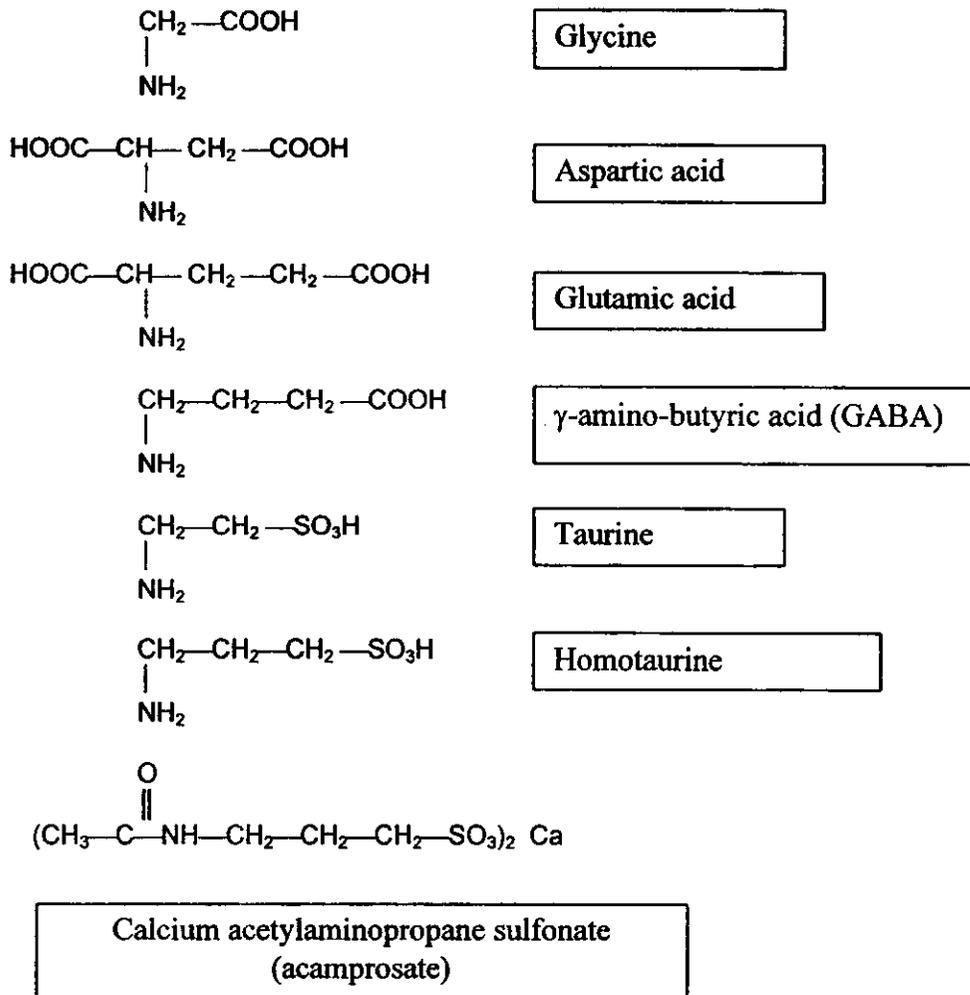
2.1 Pre-clinical Efficacy

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

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

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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

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level an allosteric interaction with a polyamine binding site on the NMDA receptor complex is the current best explanation for this action of acamprosate.

At present, the state of alcohol dependence is believed to result in disturbance of the fundamental balance in the brain between the inhibitory transmitter GABA and the excitatory transmitter glutamate. Acamprosate appears to restore this balance, with a major mechanism being the normalization of function of glutamate receptors of the NMDA receptor subtype.

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

2.2 Pre-Clinical Safety

(This material is taken from the Pharmacology/Toxicology Review prepared by Drs. Kathleen Haberny and Timothy McGovern.)

2.2.1 Safety pharmacology

Acamprosate had negligible central nervous system activity except for a slight increase in spontaneous activity in rats and attenuation of induced hyperactivity in mice. No cardiovascular effects were noted in normal rats, but acamprosate reduced blood pressure in spontaneously hypertensive rats. Cardiovascular effects were minor in dogs, and included slight decreases in heart rate and respiratory rate, and slightly increased PR and QRS intervals when administered intravenously; no effects on QT interval were noted. Oral administration induced sporadic instances of 2nd degree auriculo-ventricular heart block and ventricular premature beat after 13 weeks, but not 26 weeks, of treatment in dogs.

2.2.2 General toxicology

Studies up to 6-months duration were performed in rats and dogs. In rats, effects on renal function including decreased urinary volume (up to 37%) and significant increases in urine calcium (2-13 fold) were observed in a 3-month oral toxicity study. Other kidney effects included distension of kidney tubule sections from coagulum accumulations attributed to early senile nephrosis in 3/12 animals at the high dose of 2400 mg/kg. In the 6 month study, 22 of 60 animals died between weeks 15 and 26 of dosing at the highest dose (2400 mg/kg). Associated renal lesions in 15 of these animals included vacuolation, calculi, tubular ectasia, pelvic distension, intracellular mineralization and epithelial atrophy. Other target organs included heart (mineralization, myolysis, fibrosis, myocarditis and pericarditis), brain (thrombus, vacuolation) and GI tract (mineralization, hyperkeratosis, dyskeratosis, inflammation). Grossly, GI changes included hypertrophy, gas, distension, and liquid

contents. Again a 2-20 fold increase in urine calcium was noted. A NOAEL was not identified in this study and was < 320 mg/kg.

In the 6-mos dog study, observations included diarrhea, cardiac abnormalities described earlier, increased urinary calcium. No definitive target organs were identified in dogs at doses up to 1000 mg/kg. The sponsor has committed to performing an additional toxicity study in dogs in order to characterize the toxicity profile in a non-rodent species.

2.2.3 Genetic toxicology

Acamprosate was negative for mutagenicity in the Ames test, and for clastogenicity in the Chromosome aberration assay in human lymphocytes and in the *in vivo* Mouse Micronucleus test. Equivocal findings were observed in a point mutation assay using Chinese hamster V79 cells treated with 100-3000 mg/plate without metabolic activation; results were negative with metabolic activation. However, because of the positive findings, the genotoxic potential of acamprosate can not be ruled out. The highest concentrations used in the chromosome aberration assay and point mutation assay using Chinese hamster V79 cells and incubation times in the former assay with metabolic activation appear to be inadequate. Thus, the genotoxic potential of Acamprosate has not been fully evaluated. The *in vitro* chromosome aberration assay and point mutation assay using Chinese hamster V79 cells should be repeated using currently accepted dosing criteria and incubation times.

2.2.4 Carcinogenicity

Under the conditions tested, acamprosate was negative for carcinogenicity in rats. The study in mice is considered to be inadequate to provide a definitive assessment of the carcinogenic potential. The results of the carcinogenicity studies in mice and rats were presented to the Executive CAC committee on March 19, 2002. The committee concluded that the doses used in the rat study were only marginally adequate based on ICH criteria, but the study can be accepted based on overall toxicity and renal effects, particularly in the male rats. The carcinogenicity study in mice is unacceptable due to inadequate dose selection, based on lack of evidence for an MTD. In addition, the mouse study results were confounded by nematode infestation and histopathology evaluation was conducted on an inadequate number of low- and mid-dose animals. The committee recommended that the sponsor repeat the mouse carcinogenicity study.

2.2.5 Reproductive toxicology

Acamprosate did not affect fertility in mice or rats at doses up to 2400 mg/kg or 1000 mg/kg, respectively. No effects on embryo-fetal development were observed in mice or rabbits at doses up 2400 mg/kg or 1000 mg/kg, respectively. However, developmental effects in rat pups were observed at doses of 300 mg/kg or greater and included malformed iris, retinal dysplasia, retroesophageal subclavian artery, and hydronephrosis. No effects were noted at the low-dose of 50 mg/kg. In peri- and post-natal studies, an increase in the number of maternal mice delivering still-born offspring and the number of still-born offspring was increased at doses of 960 and 2400 mg/kg. No effects were noted at the low dose of 320

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mg/kg or in the study performed in rats up to 2000 mg/kg. The findings summarized above indicate that acamprosate should be classified as a Pregnancy Category C. However, the findings in animals should be considered in relation to known reproductive effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans.

2.2.6 Special toxicology

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

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

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

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

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

3.1 Pharmacokinetics

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

The oral absolute bioavailability of acamprosate tablets after single-dose administration has been shown to be approximately 11%. After administration of two 333 mg tablets, the C_{max}

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of approximately 94 ng/ml is reached at T_{max} of 4.5 hours. After multiple-dose administration of 666 mg t.i.d., the C_{max} is approximately 353 ng/ml and steady state is reached within 5 days.

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

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

Food effect studies showed that the C_{max} of single-dose acamprosate was decreased by 45% and the AUC was decreased by 23% in the presence of food. However, the effect of food in the multiple-dose, steady-state context has not been evaluated and most clinical trials specifically instructed subjects to take acamprosate with meals.

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

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

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

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

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

Various interaction studies have been performed with acamprosate, relevant to the treatment of alcohol-dependent patients. There was no significant effect of multiple doses of

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

3.2 Pharmacodynamics

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

3.2.1 Effect of Acamprosate on EEG

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

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

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

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

- Two reference recordings on successive days before acamprosate administration (Period 1).