1. • E.K. Weibel et al., J. Antibiot. (Tokyo) 40:1081-1085 (1987)
   • E. Hochuli et al., Ibid 40:1086-1091 (1987)
   • P. Hadváry et al., JBC 266:2021-2027 (1991)

2. According to a review by Carey and Hernell [Seminars GI Dis. 3:189-208 (1992)] in healthy human adults, the level of enzyme secreted into the intestinal lumen was calculated to be in 1,000-fold excess of what would be required for hydrolysis of the 100 g of TG ingested daily. However, the pancreas is not fully developed at birth, resulting in much lower postprandial luminal levels of pancreatic enzymes during the neonatal period, especially in preterm newborns. Furthermore, the physiological TG-substrate of breast-fed newborns, i.e., the human milk fat globule is a poor substrate for colipase-dependent lipase even in the presence of required cofactors, i.e., colipase and bile salts (vide infra).

3. In contrast to the lipase itself, colipase is secreted as a proform, procolipase or colipase 101 that is cleaved by trypsin to colipase 96 [B. Borgström et al., FEBS Lett. 108:407-410 (1979)].

4. The principal function of colipase is to induce tight-binding of pancreatic lipase to the emulsion interface in the presence of physiological levels of bile-salts. Furthermore, the active colipase is capable of penetrating phospholipid-covered TG emulsions in contrast to procolipase. It has been claimed that the N-terminal pentapeptide cleaved off by trypsin and named enterostatin may be involved in control of satiety [C. Erlanison-Albertsson and A. Larsson, Biochimie 70:1245-1250 (1988)].

5. Results of studies by Khouri et al. [Gastroenterology 96:848-852 (1989)] indicate that in adult patients with pancreatic insufficiency, the fecal TG content does not differ from the controls. However, a fivefold to sixfold increase in fecal FA content in patients with pancreatic insufficiency was revealed. [As patients with maldigestion do not excrete an excess of undigested TG, it is not possible to differentiate maldigestion from malabsorption by quantifying fecal TG and FA].

6. Depending on the animal species and substrates used for characterization, many names have been used to denote what now appears to be the same enzyme, i.e., pancreatic esterase, cholesterol esterase, cholesterol ester hydrolase, carboxylic ester lipase, retinyl ester hydrolase, lysophospholipase, etc. During evolution, this lipolytic enzyme seems to have been a primitive lipase and preceded the colipase dependent pancreatic lipase. As with BSSL, CEH shows lack of specificity toward both fatty ester chemistry and physical-chemical state of substrates and hydrolytic rates decrease in the rank order, micelles are hydrolyzed faster than emulsions, which are hydrolyzed faster than liquid crystals [M. Lindström et al., BBA 959:178-184 (1988); K. Reue et al., J. Lipid Res. 32:267-276 (1991)].

7. This is the only "lipase" secreted in proenzyme form. The active enzyme catalyzes the specific hydrolysis of *sn*-2 FA ester linkages in a variety of phosphoglycerides but it is without effect on sphingolipids, which appear to be hydrolyzed by an enzyme or enzymes on the brush-border of absorptive cells -- possibly the poorly characterized lactase-ceramidase complex. Pancreatic phospholipase A_2 has an absolute requirement for Ca^{2+} ions that bind in a 1:1 stoichiometry to substrate and enzyme at its active site. The enzyme rapidly hydrolyzes phospholipid preferentially in micelles, but also in liquid crystals and on emulsion surfaces.

8. • Y. Huang and D.Y. Dui, J. Lipid Res. 31:2029-2037 (1990)
   • H.J. Aho et al., Int. J. Pancreatol. 5:123-134 (1989)
   • P. Lechêne de la Porte, BBB 920:237-246 (1987)

9. • M.S. Bosner et al., Biochemistry 85:7438-7442 (1988)

10. B. Bergström and H.L. Brockman. Lipases. Amsterdam, Elsevier Science, pp. 1-527 (1984)

11. [Refo #86 in the Carey and Hernell review (locus cited) (1992)].

12. • C. Güzelhan et al., Int. J. Obesity 15(Suppl.1):29 (1991)
    • J. Hauptman et al., AJCN 55:309S-313S (1992)

13. H.B. McMichael, Digestion and malabsorption of fat, in Bouchier IAD, Allen RN, Hodgson HJF (eds): Textbook of Gastroenterology, London, England, Balliére, pp 367-375 (1984).

14. J.S. Trier et al., Gastroenterology 75:307-316 (1978)

15. G. Neale: Bacteriology of the small gut and bacterial overgrowth, in Bouchier IAD, Allen RN, Hodgson HJF (eds): Textbook of Gastroenterology: London, England, Balliere, pp. 487-510 (1984)

16. J.B. Thompson et al., JLCM 73:521-530 (1969)

17. O. Hernell et al.: Human milk enzymes with emphasis on the lipases, in Lebenthal E (ed): Textbook of Gastroenterology and Nutrition in Infancy. New York, NY. Raven, pp 209-217 (1989).

18. M.C. Carey et al., Annu. Rev. Physiol. 45:651-677 (1983).

19. P.J. Thomas, Gastroenterology 62:430-435 (1972).

20. H.V. Ammon and S.F. Phillips, Gastroenterology 65:744-749 (1973).

21. T.S. Gaginella et al., DDS 20:1171-1177 (1975).

22. J.H. Weisburger and E.L. Wynder. Etiology of colorectal cancer with emphasis on mechanism of action and prevention. In: V.T. DeVita et al (eds.). Important advances in oncology, J.B. Lippincott, Philadelphia, pp. 194-220 (1987)
- H.L. Newmark et al., JNCI 72:1323-1335 (1984)
- M.J. Hill et al., Lancet, ii:185-186 (1987)
- B.D. Reddy et al., Cancer Res. 37:3238-3242 (1977)
- P. Senesse et al., Gastroenterology, 108:A536 (1995).

23. [Hl. Holubec et al., Gastroenterology 106:A393 (1994); P.K. Bamberger et al., Gastroenterology 108:A447 (1995); D. Earnest, Gastroenterology 108:A463 (1995); R. Wali et al., Gastroenterology 108:A550 (1995); D. Peters et al., Gastroenterology 110:A576 (1996); T. Ochsenkühn et al., Gastroenterology 110:A571 (1996)].

24. Experiments reported by Reddy et al. have shown that CA, CDCA, DCA and LiCA, but not cholesterol, cholesterol epoxide, triol or their microbial products exert a tumor promoting effect in MNNG-induced colon carcinogenesis.

25. According to the work of L.L. Shekels et al. [JLCM 127:57-66 (1996)] BAs do not stimulate cell growth in undifferentiated or differentiated colon cancer cells lines, in contrast to normal colonic epithelium *in vivo*. BA cytotoxicity correlated with the relative hydrophobicity (TUDCA alters the cytotoxicity of DCA *in vitro*) *in vitro*.

26. It has been proposed that SCFAs, especially n-butyric acid, may have antineoplastic properties by inhibiting cell proliferation and inducing cell differentiation [J.J. Dang et al., Gastroenterology 106:A380 (1994); G. D'Argenio et al., Gastroenterology 106:A380 (1994); S..J.D. O'Keefe et al., Gastroenterology 108:A520 (1995); M. Barshishat, Gastroenterology 110:A489 (1996); L.J. Guyver et al., Gastroenterology 110:A524 (1996); I. Nordgaard, Gastroenterology 110:A569 (1996); B. Schwartz et al., Gastroenterology 110:A591 (1996); W. Scheppach et al., Gastroenterology 110A589 (1996); F. Richter et al., Gastroenterology 110:A583 (1996)].

27. Analysis of samples for BrdU and PCNA was conducted at the MD Anderson Cancer Center, Houston, TX. Two subjects' (#4 and #9) biopsy specimens were not scorable for the BrdU marker at discharge.

Analysis of samples for WCMC was conducted at Denver Dept. of Veteran Affairs Med. Center, Univ. of Colorado Sch. of Med., Denver, CO.

28. Fecal samples were analyzed by Medi-Lab, Copenhagen, Denmark.

29. In dairy cows, based on disappearance of LCFA from the large intestine, P.D. Møller [Acta Vet. Scand., Suppl.86:222-224 (1989)] has presented data that indicate either a transcellular absorption of LCFA from the large intestine or an oxidation and shortening of FA by bacteria in the hindgut for their energy supply. Studies on human colonic absorption of LCFA are not available.

30. Listed below are pertinent although selective references to the relationship between BAs and colon cancer:

- C.C. Boring et al., CA Cancer J. Clin. 44:7-26 (1994)
- D.J. Ahnen, J. Cell Biochem. 16G(Suppl):143-150 (1992)
- E. Bayerdörffer et al., Gastroenterology 104:145-151 (1993)
- E. Bayerdörffer et al., Digestion 55:121-129 (1994)
- J.W. Cook and G.A. Hazelwood, Chem. Ind. Rev. 11:758-759 (1933)
- M.J. Hill; Mechanisms of colorectal carcinogenesis IN: Diet and Human Carcinogenesis, J.V. Joossens (Ed.), Elsevier Scientific Publishers, pp 149-163 (1985)
- M.J. Hill, Eur. J. Cancer Prev. 1(Suppl 2):69-72 (1991)
- B.S. Reddy and E.L. Wynder, Cancer, 39:2533-2539 (1977)
- N. Tanida et al., Gut 25:824-832 (1984)
- M.J. Hill et al., Br. J. Surg. 72:5123-5124 (1985)
- B.S. Reddy et al., Cancer Res. 37:3238-3242 (1977)
- M. Wilpart et al., Carcinogenesis 4:45-48 (1983)
- K. Suzuki and W.R. Bruce, JNCI 76:1129-1132 (1986)
- J. Summerton et al., Digestion 31:77-81 (1985)
- B.S. Reddy et al., Prev. Med. 17:432-439 (1988)
- I.P. van Munster et al., Eur. J. Cancer Prev. 1(Suppl 2):35-44 (1991)
- B.S. Reddy et al., Gastroenterology 102:1475-1482 (1992)
- I. Makino et al., J. Lipid Res. 19:723-728 (1978)

31. This is also true for neoplasia in UC. Woolrich et al. studied the subsite distribution of dysplasia among patients with long-standing UC. Of 28 sites in which colonoscopy surveillance biopsy showed the presence of dysplasia, 19 (68%) were in the rectosigmoid colon. Although colon cancer mainly occurs in the distal part of the colon, cytolytic activity of fecal water is higher and AP activity (indicating degree of epithelial damage). is more pronounced after right than after left hemicolectomy. [This may explain in part the preponderance of tumors in the distal colon as compared to the proximal colon, especially after hemicolectomy [J.H. Kleibeuker et al., Gastroenterology 106:A403 (1994).] Right sided location as well as earlier age of adenoma diagnosis in probands are independent risk factors for an increased familial risk of colorectal cancer [A.G. Zauber et al., Gastroenterology 106:A455 (1994)]. In a study of colonic mucosal proliferation and DCA, T. Ochsenkühn et al. [Gastroenterology 110:A571 (1996)] found that serum DCA levels correlated significantly with the respective proliferation rates in the individual colonic segments (ascended, descended and sigmoid) but no correlation was found for the rectum and the cecum. Finally a historical prospective study conducted among residents of Rochester, MINN who underwent cholecystectomy concluded that the statistically significant increase in relative risk was observed only in women and was more marked for right-sided colon cancer [D.A. Linos et al., Lancet ii:379-381 (1981)]. Ornithine Decarboxylase activity (proposed as a marker of uncontrolled cell proliferation), was significantly higher than in the left colon or rectum [S. Civitelli et al., Gastroenterology 110:A504 (1996)].

32.

- B.N. Ames and L.S. Gold, Science 249:970-971 (1990)
- Ibid. Proc. Natl. Acad. Sci, U.S.A. 87:7777-7781 (1990)
- S.M. Cohen and L.B. Ellwein. Science 249:1007-1011 (1990)
- S.M. Cohen et al., Mod. Pathol. 4:371-382 (1991)
- S.M. Cohen and L.B. Ellwein, Cancer Res. 51:6493-6505 (1991)
- S. Preston-Martin et al., Cancer Res. 50:7415-7421 (1990)
- P. Grasso and M. Sharratt, Annu. Rev. Pharmacol. Toxicol. 31:253-287 (1991)

33. Colonic preparation with oral senna extract (anthraquinone glycosides) should be avoided when proliferation studies of the colon are to be performed [J.H. Kleibeuker et al., JNCI 87:452-453 (1995)].

34. The COX-2 gene has been shown to be expressed at high levels in 85% of human adenocarcinomas and 45% of human adenomas. COX-2 expression is increased in intestinal tumors that develop in Min mice and carcinogen-treated rats. Treatment of these animals with many different NSAIDs results in a marked decrease in tumor multiplicity. Together, all these results make it likely that COX-2 may be involved in the adenoma-to-carcinoma sequence of events and that increased expression of COX-2 may result from an inability of the *APC* gene product to carry out its normal function. If this hypothesis proves to be correct, the clinical implications would be profound since new drugs have recently been developed that are highly selective COX-2 inhibitors that suppress polyp formation [M. Oshima et al., Cell 87:803-809 (1996); J. Vane, Nature 367:243-249 (1994)].

Table 8: Summary of evaluable drug interaction studies performed with orlistat. Further details may be found in the Appendix.

Drug	Orlistat Dose	Design	Cmax				AUC		
			n	Orlistat (Mean ± SD)	Placebo (Mean ± SD)	Mean Ratio (90%CI)	Orlistat (Mean ± SD)	Placebo (Mean ± SD)	Mean Ratio (90%CI)
Digoxin	120 mg	crossover	12	2.11±0.65	2.20±0.51	0.95 (0.85, 1.05)	22.9±4.8	24.2±6.2	0.99 (0.85, 1.15)
Warfarin	120 mg	crossover	12	R:1.73±0.35 S:1.64±0.30	R:1.62±0.22 S:1.61±0.22	R:1.06(0.99,1.14) S:1.01(0.93,1.10)	R:96.2±31.2 S:69.6±24.3	R:97.1±29.9 S:68.7±22.5	R:0.99(0.94,1.05) S:1.00(0.96,1.05)
Phenytoin	120 mg	crossover	12	3.97±0.46	3.81±0.74	1.24(1.06,1.44)*	136±33	136±37	1.00(0.96,1.05)
Nifedipine GITS	120 mg	crossover	17	25.9±8.9	25.1±10.1	1.07(0.87,1.32)	702±280	654±257	1.11(0.85,1.44)
Oral C'ceptives	120 mg	crossover	20	na	na	E:1.08(0.93,1.26) P:1.09(0.90,1.33)	na	na	E:0.97(0.89,1.06) P:0.96(0.89,1.05)
Ethanol	120 mg	parallel	20‡	0.44±0.10	0.43±0.06	1.01(0.89,1.15)	62.6±10.6	63.9±9.2	0.95(0.84,1.07)
Glyburide	80 mg	crossover	12	136±42	165±107	0.89(0.64,1.25)	701±252	892±502	0.85(0.58,1.25)
β-carotene 30 mg	120 mg	crossover	12	126±90	221±146	0.72(0.32,1.09)	6.65±5.2	10.8±7.2	0.66(0.30,1.47)
β-carotene 60 mg	120 mg	crossover	12	212±106	298±159	0.72(0.54,0.96)	11.4±6.2	16.2±10.2	0.70(0.51,0.98)
β-carotene 120 mg	120 mg	crossover	12	262±180	346±61	0.64(0.44,0.93)	14.7±10.9	19.9±3.6	0.62(0.42,0.90)
Vit. E acetate	120 mg	crossover	12	15.3±5.9	25.3±6.8	0.57(0.44,0.75)	569±319	1207±379	0.40(0.28,0.59)
Pravastatin	120 mg	parallel	12†	43.9±20.1	34.8±13.3	1.23(0.91,1.66)	89.2±36.9	66.9±25.8	1.34(1.00,1.79)

na: not available since several different products with differing amounts (and types for progestins) of hormones were used. E:estradiol, P: progestins
* first period data only due to sequence effect
† Group B only; day 1 (without orlistat) vs. Day 10 (with orlistat). Group A showed no accumulation upon multiple dosing.
‡ n=10 per arm; an additional 10 subjects received placebo of both drugs

VII. Pharmacokinetic / Pharmacodynamic Relationships

Dose-Response (Fecal Fat Excretion) Relationship

The amount of ingested fat excreted in the feces after drug administration was utilized as a quantitative pharmacological endpoint for evaluating the orlistat effect; whether or not fecal fat excretion is a valid surrogate marker for clinical efficacy (i.e. weight loss) is unknown. A simple Emax model that included a basal value was used in modeling the dose-response curve of the relationship between orlistat daily dose and fecal fat excretion:

$$E = Eo + Emax \cdot D / (ED50 + D)$$

where E is the intensity of the effect produced by orlistat treatment expressed as the percent of ingested fat excreted, Eo is the intensity of the basal effect (no drug), Emax is the maximum attainable intensity of effect produced by orlistat alone, D is the orlistat daily dose (mg/day) administered as three divided doses, and ED50 is the orlistat daily dose which produces 50% of the maximum effect (table 9).

Figure 4 represents 169 observations of orlistat dose-response relationship from a total of 171 normal or obese male and female volunteers in 11 phase I orlistat clinical studies conducted in the U.S. over a 2-yr period. These studies used a variety of formulations in hard gelatin capsules, with doses ranging from 0 (placebo) to 1200 mg/day administered for 9-10 days. Mean daily fecal fat excretion was calculated by averaging the daily fecal fat excreted (relative to ingested fat) from day 3 through the last day of dosing.

Table 9. Fitted results based on the Emax model

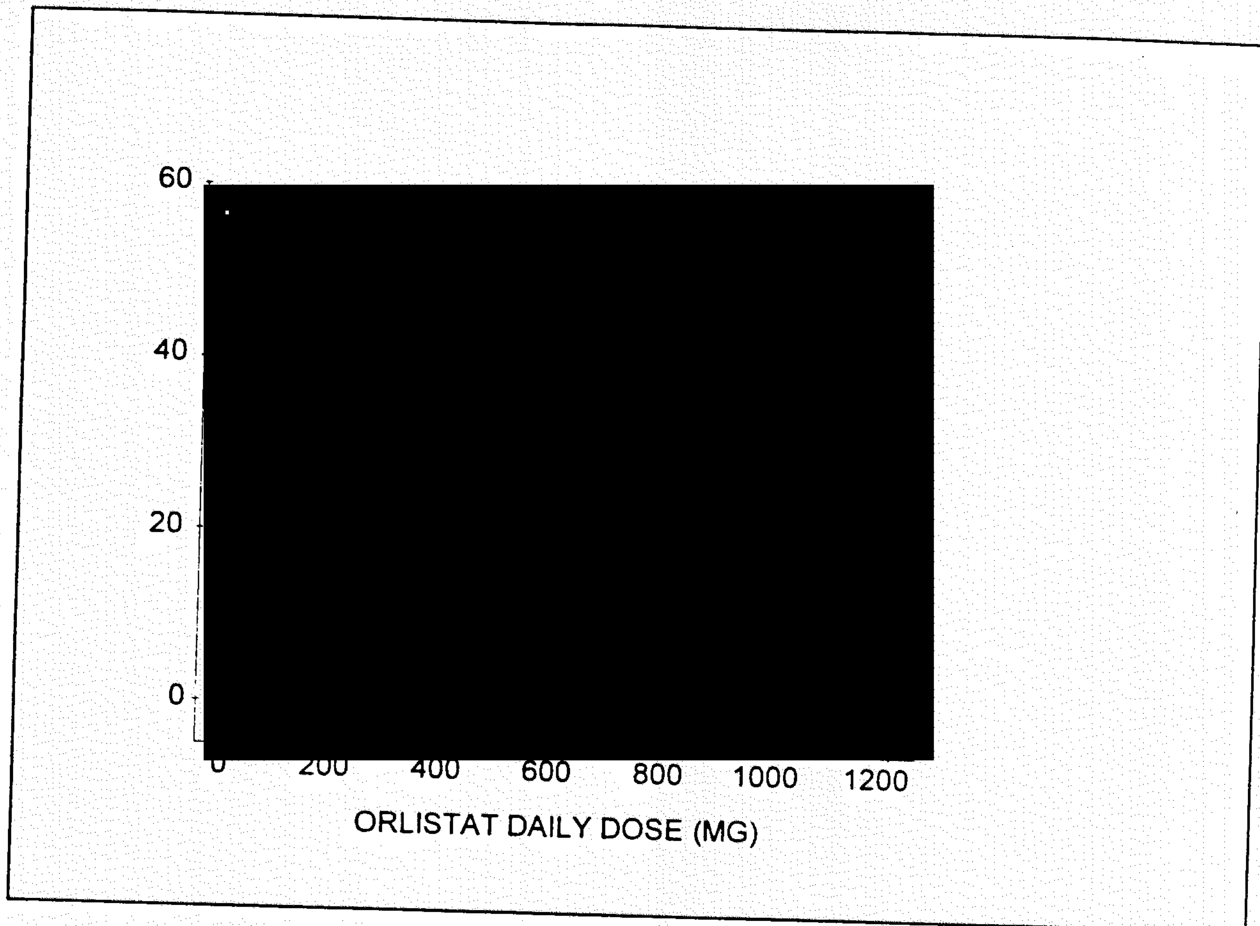
Parameter[a]	Mean	Standard Error	95% Confidence Interval
Eo (%)	5.29	1.05	3.21-7.36
Emax (%)	27.1	2.9	21.5-32.8
ED50 (mg/day)	98.1	34.4	30.2-166.0

[a] See text for explanation of parameters

The maximum percentage of ingested fat excreted in the feces totaled approximately 32% (Eo + Emax), regardless of the amount of fat ingested (within the range studied, i.e., 50 to 80 g/day). There were, according to the publication, no differences in data between healthy and obese, or male and female, subjects.

BEST POSSIBLE

APPEARS THIS WAY ON ORIGINAL



[redacted]

Figure 4. Dose-Response Relationship for Orlistat in Human Volunteers. The effect is the percentage of ingested fat excreted, referred to as fecal fat excretion percentage (vertical axis). Both individual data (open circles) and a best fit of the curve predicted for the population with the Emax model (continuous line) are shown. From Clin Pharmacol Ther, 56:82-5, 1994.

APPEARS THIS WAY ON ORIGINAL

COMMENTS TO BE SENT TO THE SPONSOR:

1. Although the warfarin-orlistat interaction study showed that orlistat had no effect on the pharmacokinetics of either stereoisomer of warfarin, the ratio of the K1 treatment means and 90% confidence interval (0.69 [0.39, 1.25]) suggest that there may be some adverse effect on K1 absorption. Based on the short duration of the study and the suggested effect on vitamin K absorption, an interaction with warfarin (based on affecting the absorption of vitamin K with a resulting increase in prothrombin time) can not be ruled out. It is recomended that the labeling reflect this uncertainty. In addition, we request that a study be performed post-approval examining the effect of orlistat on plasma vitamin K and prothrombin time in patients on chronic warfarin therapy.

2. The dose of vitamin A used in Study N130970 was inadequate to raise retinol levels significantly above baseline, so no conclusions may be drawn from this study. In view of the ability of orlistat to decrease vitamin E and β-carotene absorption, it appears likely that it might also inhibit vitamin A absorption. It is recommended that the labeling reflect this conclusion (see Labeling Comments).

3. As cyclosporin is dependent on dietary fat for adequate absorption, concomitant administration of orlistat and cyclosporin might be expected to decrease the absorption of cyclosporin, which could be associated with rejection in transplant patients. Although it is unclear whether orlistat would ever be prescribed in a transplant patient, the potential dire consequences of decreased cyclosporin levels suggests that orlistat be contraindicated in patients taking cyclosporin. This should be noted in the labeling.

[redacted]

LABELING COMMENTS:

(Also, see revised labeling, page 86-104.)

[redacted]

., DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

/S/

[redacted] 03/21/97

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[redacted] 3/21/97

APPEARS THIS WAY ON ORIGINAL

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 3/21/97

/S/

FT initialed by Hae-Young Ahn, Ph.D., Team Leader [redacted] 3/21/97

Attendees for Clin/Bio Pharm Briefing (03/14/97): M Chen, Ahn, Mehta, Collins, Huang, W Gillespie, Lazor, Balian

cc: NDA 20-766(orig.,1 copy), HFD-510(Colman, Hess, Hertig), HFD-340(Vishwanathan), HFD-870(Shore, Ahn, Fossler, M. Chen), CDR (Barbara Murphy).

/S/

[redacted]

RESULTS

Drug Name:	Atenolol (P-7155)	
Dose/Trade name:	100-mg Tenormin® tablet	
Treatment:	Without Orlistat	With Orlistat
C_{max} (ng/mL)	578 ± 116	636 ± 236
t_{max} (h)	2.14 ± 0.68	1.77 ± 0.40
$t_{1/2}$ (h)	7.17 ± 1.36	7.22 ± 0.76
AUC (ng·h/mL)	4258 ± 975	4741 ± 1260

APPEARS THIS WAY ON ORIGINAL

CONCLUSION/LABELING CLAIM:

No statistically significant differences of the absorption and elimination kinetics of atenolol could be detected before and during multiple dose treatment with orlistat.

REVIEWER'S COMMENTS

1) This study is too small to allow any conclusions regarding the effect of orlistat on atenolol PK.

APPEARS THIS WAY ON ORIGINAL

Appendix 1.5.1.2. Influence of Ro 18-0647 (THL) on Pharmacokinetics of Captopril in Hospitalized Healthy Male Volunteers (P-7159)

VOLUME:

OBJECTIVES:

To evaluate the absorption and disposition kinetics of captopril before and after administration of THL 50 mg tid for 8 days in healthy male volunteers.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Captopril: Lopirin® 50 mg tablet containing 50-mg captopril, batch no. 9A 1948

THL: hard gelatin capsule (Ro 18-0647/015, batch no. GMZ 657 D02) containing 50 mg THL

STUDY METHODS:

(a) Design: Open-label, sequential design with oral single dose administration of 50 mg captopril before (Day 1) and after (Day 9) multiple dose treatment with THL tid for 7 1/3 days (Days 2 - 9). On the last day of orlistat treatment in this second captopril pharmacokinetic study, only the morning dose of orlistat was administered.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
7/0	19-37	55-88	--

(c) Sampling times:

Days 1 and 9: plasma samples were collected at 0 h (predose); and 15, 30, 45, 60, 90, 120, 150 min, 3, 4, 6, 8, 10, 12, and 24 h postdose of captopril.

ASSAY:

[redacted]

DATA ANALYSIS:

No pharmacokinetic evaluation was performed due to lack of valid analytical results.

CONCLUSION/LABELING CLAIM:

Although profiles of plasma concentrations of captopril *vs.* time were similar before and after multiple doses of 50 mg tid THL for 7 1/3 days, further statistical analyses were not performed due to assay technical problems.

REVIEWER COMMENTS

1) Not reviewed due to assay problems.

APPEARS THIS WAY ON ORIGINAL

Appendix 1.5.1.3. Influence Of Ro 18-0647 (THL) on the Pharmacokinetics of Furosemide in Healthy Male Volunteers (P-7158)

VOLUME: 1.138

OBJECTIVES:

To evaluate the influence of multiple dose treatment with THL 50 mg tid for 8 days on the pharmacokinetics of furosemide in healthy male volunteers.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Furosemide: Lasix® 40-mg tablet, batch no. 88DL06358

THL: hard gelatin capsule (Ro 18-0647/015, batch no. GMZ 657 D02) containing 50 mg THL

STUDY METHODS:

(a) Design: Open-label, sequential design with oral single dose administration of 40 mg furosemide before (Day 1) and on the last day (Day 9) of multiple dose treatment with THL 50 mg tid for 8 days (Days 2 - 9).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
6/0	21-29	70-77	--

(c) Sampling times:

Days 1 and 9: plasma samples were collected at 0 h (predose): and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 h postdose of furosemide

ASSAY:

[redacted]

DATA ANALYSIS:

Paired t-test of furosemide pharmacokinetic parameters determined by model independent methods.

RESULTS

Drug Name:	Furosemide (P-7158)	
Dose/Trade name:	40-mg Lasix® tablet	
Treatment:	Without Orlistat	With Orlistat
C_{max} (ng/mL)	369 ± 111	235 ± 89
t_{max} (h)	2.15 ± 1.1	2.33 ± 0.62
$t_{1/2}$ (h)	3.60 ± 2.1	4.80 ± 2.1
AUC (ng·h/mL)	1046 ± 236	1050 ± 193

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE

CONCLUSION/LABELING CLAIM:

Multiple dose treatment with 50 mg tid THL did not significantly influence the pharmacokinetics of furosemide.

REVIEWER COMMENTS

1) Again, this study is too small to allow any conclusions to be drawn about the effect of orlistat on furosemide PK.

APPEARS THIS WAY ON ORIGINAL

Appendix I.5.1.4. Influence of Ro 18-0647 (THL) on the Pharmacokinetics of Nifedipine in Hospitalized Healthy Male Volunteers (P-7157)

VOLUME: 1.137

BEST POSSIBLE

OBJECTIVES:

To investigate the influence of multiple dose treatment with THL 50 mg tid for 8 days on the absorption and disposition kinetics of nifedipine in healthy male volunteers.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Nifedipine: ADALAT retard tablet, batch no. GJ 041

THL: hard gelatin capsule (Ro 18-0647/015, batch no. GMZ 657 D02) containing 50 mg THL

STUDY METHODS:

(a) Design: Open-label, sequential design with oral single dose administration of nifedipine before (Day 1) and after (Day 9 or Day 11) multiple dose administration of THL tid for 7 1/3 to 9 days (Days 2 - 9 or 11). On the last day of orlistat treatment in this second nifedipine pharmacokinetic study, only the morning dose of orlistat was administered.

(b) Demographics (PK):

Gender (M/F)	Age (yr)	Weight (kg)	Origin
8/0	20-38	62.5-86.5	--

(c) Sampling times:

Days 1 and 9: plasma samples were collected at 0 h (predose); and 15, 30, 45 min, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h postdose of nifedipine.

ASSAY:

[redacted]

DATA ANALYSIS:

Paired t-test of nifedipine pharmacokinetic parameters determined by model independent methods.

RESULTS

Drug Name:	Nifedipine (P-7157)	
Dose/Trade name:	20-mg ADALAT retard tablet	
Treatment:	Without Orlistat	With Orlistat
C_{max} (ng/mL)	67.1 ± 24.5	63.8 ± 31.7
t_{max} (h)	1.31 ± 0.58*	2.13 ± 0.99*
$t_{1/2}$ (h)	3.18 ± 1.36	2.94 ± 1.38
AUC (ng·h/mL)	294 ± 141	282 ± 153

*$p < 0.05$ (student t–test): $p = 0.05$ (Wilcoxon test)

CONCLUSION/LABELING CLAIM:

No statistically significant differences in the pharmacokinetic parameters of nifedipine could be detected before and after multiple dose treatment with orlistat, except for t_{max} ($P < 0.05$); however, this difference is clinically not relevant.

REVIEWER COMMENTS:

1) Too small for meaningful conclusions. A better nifedipine study was performed using Procardia XL.

Appendix 1.5.2. Narrow Therapeutic Index Drugs

Appendix 1.5.2.1. The Effect of Orlistat (Ro 18-0647) on the Pharmacokinetics of Digoxin in Healthy Volunteers (Protocol NK14276A)

VOLUME: 1.149

BEST POSSIBLE

OBJECTIVES:

To assess the effect of orlistat (Ro 18-0647) on the pharmacokinetics of digoxin in healthy volunteers.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Digoxin: (Lanoxicaps®, Burroughs Wellcome Co.): 0.4 mg tablets, lot no. 1S5003

Orlistat: 120-mg capsules (Ro 18-0647/090, batch no. PT2157 T05, clinical order no. C169411-004)

Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T05, clinical order no. C169421-006)

STUDY METHODS:

(a) Design: Open-label, placebo-controlled, randomized, two-way crossover with an 11-day washout period between treatments. Single 0.4 mg oral doses of digoxin were administered on two occasions: on the fourth day of orlistat 120 mg and placebo tid for 6 days.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
12/0	18 - 33	58.3 - 92.9	5 White 3 Black 3 Hispanic 1 Oriental

(c) Sampling times:

Day 4: plasma samples were collected at 0 h (predose); and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, and 192 h postdose of digoxin

ASSAY:

[redacted]

DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters.

RESULTS

Comparison of the Mean Pharmacokinetic Parameters (n=12) Between the Digoxin Regimens With (A) and Without (B) Orlistat Treatment

Parameter	A	B	A/B	90% CI[b] for A/B
C_{max} (ng/mL)	2.03[a]	2.14[a]	0.95	(0.85, 1.05)
t_{max} (h)	1.7	1.4	0.3[c]	(0.0, 0.5)[c]
AUC_{0-48} (ng·h/mL)	15.2[a]	15.0[a]	1.01	(0.91, 1.12)
AUC_{0-t} (ng·h/mL)	15.7[a]	16.8[a]	0.94	(0.83, 1.06)
AUC (ng·h/mL)	22.4[a]	22.7[a]	0.99	(0.85, 1.15)
λ, (h^{-1})	0.022[d]	0.020[d]	0.002[c, d]	(-0.001, 0.005)[c, d]
$t_{1/2}$ (h)	31.5[d, e]	34.7[d, e]		

[a] *Geometric least-squares mean*

[b] *CI = confidence interval*

[c] *Difference between least-squares means (Treatment A – Treatment B)*

[d] *n = 11*

[e] *Harmonic mean.*

CONCLUSION/LABELING CLAIM:

Orlistat does not significantly alter the pharmacokinetics of a single oral dose of digoxin in healthy volunteers.

REVIEWER COMMENTS

1) Study is adequately powered, assay QC data sufficient, agree w/ conclusions.

APPEARS THIS WAY ON ORIGINAL

Appendix 1.5.2.2. Interaction Study with Ro 18-0647 and Oral Contraceptives (P-5193)

VOLUME: 1.135

OBJECTIVES:

Primary: to assess whether orlistat influences the systemic availability and ovulation-suppressing action of oral contraceptives. Secondary: to determine whether orlistat affects cytochrome P450.

INVESTIGATOR/SITE:

[redacted]

FORMULATIONS:

Oral Contraceptives: commercial combination of oral contraceptives were obtained from

local sources.

Orlistat: 120 mg capsule (Ro 18-0647/090, batch no. PT 2157 T02).

Orlistat Placebo: capsule (Ro 18-0647/098, batch no. PT2160 T08) as matching placebo.

STUDY METHODS:

(a) Design: Double-blind, randomized, placebo lead-in, placebo-controlled, 2-way crossover study with dosing of either 120 mg Ro 18-0647 tid or placebo tid on days 1-23 of the first cycle, and, separated by a placebo washout period on days 24-28, the reverse treatment on days 1-23 of the second cycle.

(b) Demographics:

	Gender (M/F)	Age (yr)	Weight (kg)	Origin
(Safety)	0/20	20-26	61.8-87.4	20 White

(c) Sampling times:

PD: Days 12 and 16 in both cycles, blood samples were collected for serum luteinizing hormone (LH) and progesterone levels.

Days 13-15 in both cycles, blood samples were collected for serum LH levels.

Days 19-23 in both cycles, blood samples were collected for serum progesterone levels.

Day 21 of both cycles, urine was collected over 24 h for urinary 6β-hydroxycortisol and free cortisol.

PK: On day 21 of both cycles, blood samples were collected predose, and 0.5, 1, 2, 3, 4, 6, 12, 16, and 24 h postdose of the contraceptive pill for serum ethinylestradiol and gestagens.

On day -8, before the evening dose of placebo, and on days 7, 14, 21, and 23 in both cycles, blood samples were collected 2-4 h after the evening dose of orlistat or placebo for plasma orlistat

ASSAY:

[redacted]

DATA ANALYSIS:

Time-averaged serum concentrations of P and LH, 24 h urinary excretion of free cortisol and 6β-HC, and the ratio of 6β-HC/free cortisol were analyzed by ANOVA. The ANOVA for crossover design was performed on values of AUC of ethinylestradiol, 3-keto-desogestrel, and of the pool of gestagens. All data were logarithmically transformed before ANOVA.

Back-transformed Mean Ratios and 90% Confidence Intervals

	Ethinyl Estradiol		Progestins	
	Cmax	AUC	Cmax	AUC
Orlistat vs. Placebo	108 (92.8, 126)	97.1 (88.7,106)	109 (89.9, 133)	96.3 (88.6,105)

CONCLUSION/LABELING CLAIM:

Orlistat did not influence the action of the oral contraceptives.

REVIEWER COMMENTS

Does not appear to be an interaction. Steroid assay data sufficient.