CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-141 and 21-176

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-141/N-000 **(X-ref NDA 21-176/N-000)**	**SUBMISSION DATE:** **30-JUL-99, 30-MAR-00(BZ), 18-APR-00(BC)**
BRAND NAME:	**Cholestagel®**
GENERIC NAME:	**Colesevelam hydrochloride 625mg oral tablet**
REVIEWER:	**Robert M. Shore, Pharm.D.**
SPONSOR:	**GelTex Pharmaceuticals, Inc., Waltham, MA**
TYPE OF SUBMISSION:	**Original NME; code 1S**

TERMS AND ABBREVIATIONS:

AUCa-b ..... Area under the plasma-concentration-time curve from time a to time b
Cmax... ..... Maximum observed concentration
DMEDP ..... Division of Metabolic and Endocrine Drug Products
DPM .... Disintegrations per minute
GC..... ..... Glycocholic acid sodium salt
GCDC . ..... Glycochenodeoxycholic acid sodium salt
MDA .... Minimum detectable activity
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
OPDRA ..... Office of Post-marketing Drug Risk Assessment
TDC..... ..... Taurodeoxycholic acid sodium salt

SYNOPSIS:

Note: The proprietary name of colesevelam is under review by DMEDP (OPDRA found both Cholestagel and Welchol to be unacceptable). However, this review will refer to colesevelam as Cholestagel.

Cholestagel (colesevelam HCl) is a polymeric bile acid sequesterant. The proposed indication is as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. It can be administered alone or with an HMG-CoA reductase inhibitor.

Results from a ^{14}C-colesevelam oral absorption study in healthy subjects indicate that radioactivities in urine and blood were below background levels. Total recovery from fecal samples for 9 days post-dose was variable (16%-100%) but probably reflects incomplete fecal collection since both blood and urine radioactivities were not significant.

Drug interaction studies with lovastatin, quinidine, valprioc acid, digoxin, warfarin, and metoprolol indicate that colesevelam does not interfere with the bioavailability of these drugs. Colesevelam did decrease the Cmax of sustained-release verapamil (Calan SR) by 31%; the clinical impact of this is unclear.

The sponsor conducted all clinical trials with a capsule formulation of colesevelam [redacted] *In vitro* bioequivalence testing, based on the 'Interim Guidance: Cholestyramine Powder *in vitro* Bioequivalence', was performed to compare the capsule and tablet formulations. Results indicate that the two formulations perform equivalently *in vitro*.

The release specifications for Cholestagel tablets include both disintegration (colesevelam is insoluble) and bile acid binding tests.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-141/N-000 (x-referenced to NDA 21-176/N-000) submitted 30-JUL-99, 30-MAR-00, and 18-APR-00. The overall Human Pharmacokinetic Section is acceptable to OCPB.

Table of Contents **Page**

(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Colesevelam is an insoluble, non-absorbed polymer which binds bile salts in the gut causing the liver to remove more cholesterol (the bile salt precursor) from the blood to convert into more bile salts thus lowering circulating cholesterol levels. Currently, other bile salt binding resins marketed in the U.S. include cholestyramine and colestipol. Colesevelam is not marketed in any other country. The proposed tablet is 625mg and dosing is 6 tablets (3.75g) once per day or 3 tablets twice a day with meals. Dosage can be increased to 7 tablets (4.375g) per day.

STUDY SUMMARY INDEX

DRUG FORMULATION AND DISINTEGRATION:

The figure below illustrates the chemical structure of colesevelam HCl. It is a white to off-white powder with a molecular formula of $(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$.

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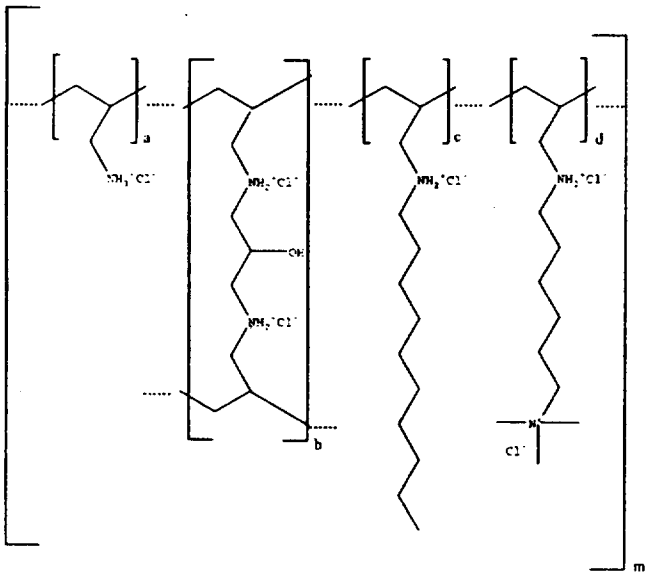

Where:

a	= number of primary amine groups	a = 0.14
b	= number of cross-linked amine groups	b = 0.12
c	= monoquat alkylated amine groups	c = 0.34
d	= decylbromide alkylated amine groups	d = 0.40
m	> 100 to indicate extended polymer network	

The capsules used in the NDA studies were 375mg colesevelam HCL and — magnesium stearate in hard gelatin capsules. An *in vivo* tolerability study was conducted with the proposed to-be-marketed tablet and was reviewed by the Medical Officer.

The table below shows the formulation for the proposed tablet:

MATERIAL	UNIT AMOUNT
Colesevelam hydrochloride, anhydrous	625 mg
—	—
Microcrystalline cellulose, NF	—
Magnesium stearate, NF	—
Silicon dioxide, NF	—

Bile acid binding capacity, for release of the tablet, is set at — grams GC per gram of polymer and — grams GCDC per gram of polymer. A colesevelam sample is prepared from tablets and sufficient sample is weighed out to contain — of colesevelam hydrochloride. The amount of GC and GCDC bound is determined by adding 40 mL of buffered solution containing GC and GCDC in concentrations of 2.5g/L and 3.5g/L, respectively, to the composite sample. After allowing equilibrium binding to occur the unbound concentration of GC and GCDC in solution is determined via — By subtracting the amount of unbound GC and GCDC in solution from the initial amount of GC and GCDC present, the bile acid salt bound to colesevelam hydrochloride can be determined. According to the sponsor, the results (see Table below) of the bile acid

binding assays for the clinical lot and NDA registration lots show that all lots meet the specification.

Since colesevelam does not dissolve, a disintegration method and specification has been proposed. The method is USP <701>, Disintegration using the disintegration apparatus ——— basket rack assembly, and wire cloth (10-mesh No. 23 (0.025-inch), woven stainless steel with plain square) with complete disintegration within — minutes. According to the sponsor, the results (see Table below) indicate that the tablets meet the specification.

(Data from Table 4.2-29)

Test	Specification	Lot Number			
		UPM9901	EK11MB	EK12MB	EK13MB
Bile Acid Binding	GC: ——— g/g GCDC: ——— g/g	0.6 1.6	0.6 1.6	0.5 1.6	0.6 1.6
Disintegration (water)	NMT — minutes	11 min	3 min	3 min	2 min

However, exactly what this table shows is questionable. Although the bile acid binding procedure was to produce a sample containing —— colesevelam HCl, the results above do not indicate whether only one sample was used or if the figures in the table are an average of multiple determinations and, if so, how many multiples? And the disintegration results also lack specifics like how many tablets were tested and, if more then one, are the figures in the table an average? These concerns were conveyed to Dean Alger at GelTex in a Tcon on 10-APR-00 and were answered in a submission on 18-APR-00:
- the bile acid binding is the mean of two replicates;
- the disintegration is the maximum time it took 6 tablets to disintegrate.

The bile acid binding spec is the same as for the drug substance and has been found to be acceptable to the Chemist. Since the capsule formulation had a disintegration of — minutes and was found to be clinically effective, the proposed specs are acceptable.

The proposed manufacturing batch size is ———tablets; drug interaction studies used batches of —— capsules.

ANALYTICAL METHODOLOGY:

[ ]

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Bioavailability

Is colesevelam absorbed after oral administration?

Study GTC48-803 explored the absorption of radiolabeled colesevelam. Sixteen healthy adults were dosed with 1.9g BID with meals of regular non-radiolabeled colesevelam for 28 days and then were administered a dose of 2.4g ^{14}C-colesevelam followed by BID doses of non-radiolabeled colesevelam for 4 more days. During the formulation process, the drug substance was _____ Thus a small residual amount of soluble, low molecular leachable material could be absorbed.

Feces and urine were collected on a 24 hour interval schedule at pre-dose, 0-24, 24-48, and so on to 96 hours for urine and 216 hours for feces. Blood was collected at predose, 4, 8, 12, 24, 48, 72, and 96 hours post ^{14}C dose.

Radioactivity in blood was non-detectable or present only in trace amounts over 96 hours.

Colesevelam hydrochloride Equivalent Concentration in Whole Blood based on Total Radioactivity

Subject Number	Drug Equivalent Concentration in Whole Blood (µg equiv./g) Time Point 4h	8h	12h	24h	48h	72h	96h
001	[						
003							
004							
005							
006							
007							
008							
009							
011							
012							
013							
014							
015							
017							
018							
020							]
Mean	0.010	0.000	0.000	0.000	0.124	0.165	0.026
SD	0.028	0.000	0.000	0.000	0.090	0.103	0.085
%CV	278	-	-	-	72	63	323
Median	0.000	0.000	0.000	0.000	0.131	0.149	0.000
Maximum	[						]
Minimum							

Radioactivity in urine was detectable and accounted for 0.05% of the administered dose.

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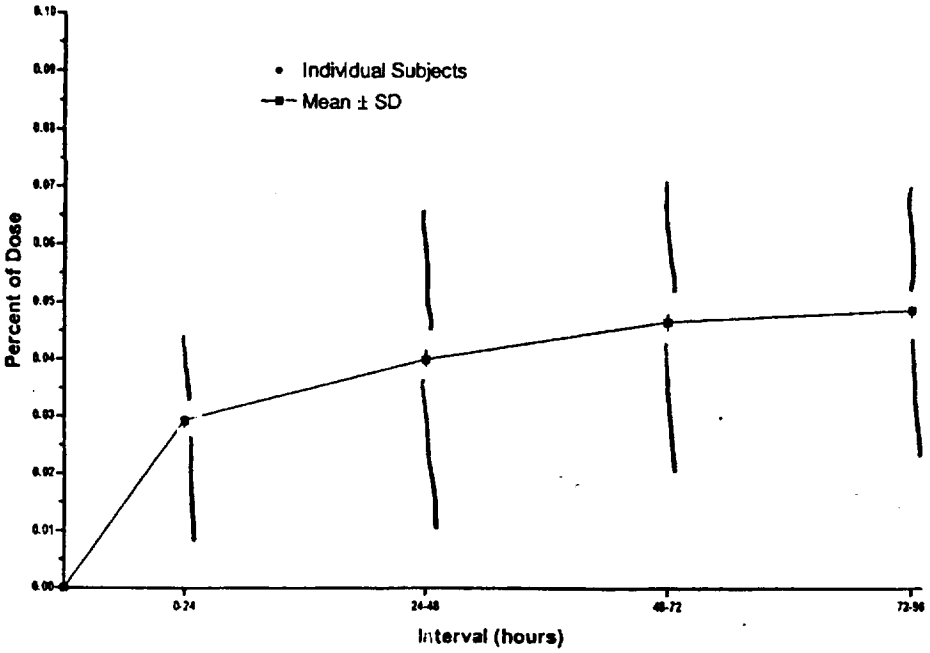
Individual and Mean Cumulative Recovery of [^{14}C] Total Radioactivity in Urine, Percent of Dose ± SD per Collection Interval



Mean Cumulative Excretion of [^{14}C]-Colesevelam hydrochloride Total Radioactivity in Urine

Subject Number	Cumulative Excretion in Urine (Percent of Dose, %Dc) Time Interval 0-24h	24-48h	48-72h	72-96h
001				
003				
004				
005				
006				
007				
008				
009				
011				
012				
013				
014				
015				
017				
018				
020				
Mean	0.029	0.040	0.047	0.049
SD	0.008	0.012	0.011	0.011
%CV	29	31	24	23

Cumulative recovery in feces of 80% or greater was observed in 50% (8/16) of the subjects. Cumulative recovery between 60-80% was observed in 38% (6/16) of the subjects. Two subjects (#003 and #020) had recoveries significantly lower than the others (< 25%). Mean cumulative recovery of radioactivity in feces

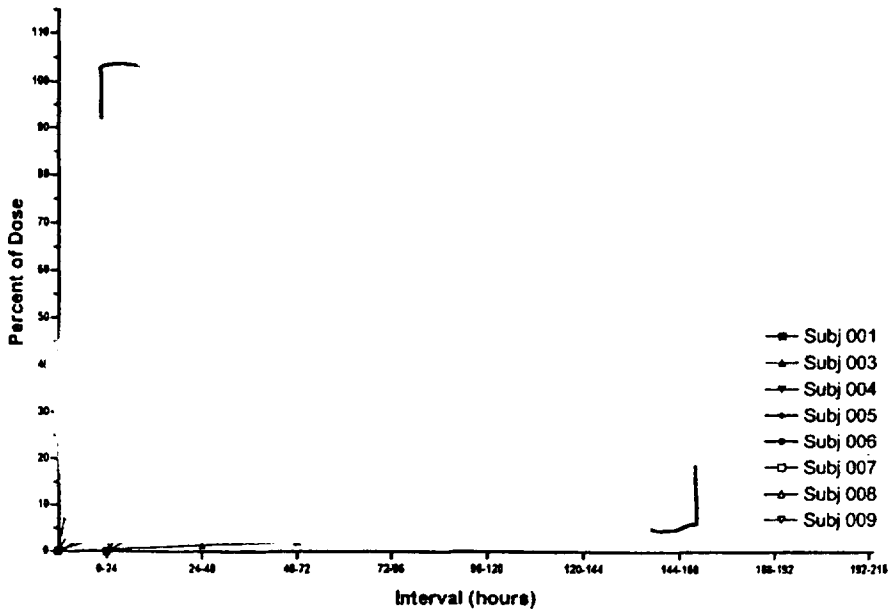
from all 16 subjects was 74.4%; excluding the two subjects who had low recovery then mean is 82.4%.

Mean Cumulative Excretion of [^{14}C]-Colesevelam hydrochloride Total Radioactivity in Feces – All Subjects

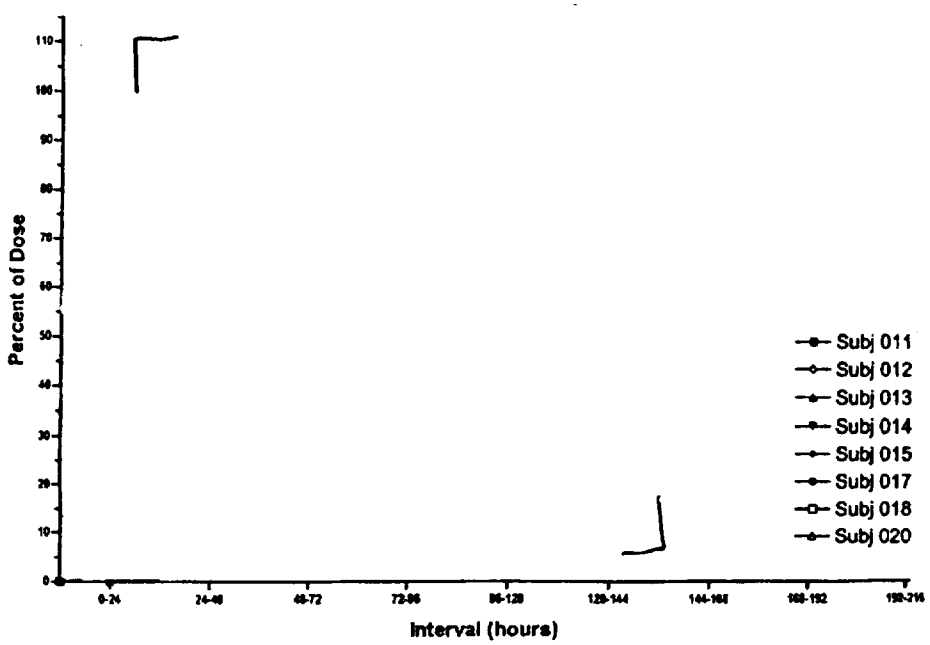
Subject Number	Cumulative Excretion in Feces (Percent of Dose, %Dc) Time Interval 0-24h	24-48h	48-72h	72-96h	96-120h	120-144h	144-168h	168-192h	192-216h
001									
003									
004									
005									
006									
007									
008									
009									
011									
012									
013									
014									
015									
017									
018									
020									
Mean	3.960	21.428	53.130	59.764	70.140	72.359	73.421	74.274	74.400
SD	13.750	23.202	35.123	34.275	28.192	27.372	27.144	26.560	26.501
%CV	347	108	66	57	40	38	37	36	36

Number of subjects with recovery greater than 90%: 5/16 or 31%
Number of subjects with recovery greater than 80%: 8/16 or 50%
Number of subjects with recovery greater than 70%: 10/16 or 63%

**Cumulative Recovery of [^{14}C] Total Radioactivity in Feces,
Subjects 001 through 009
Percent of Dose per Collection Interval**



**Cumulative Recovery of [^{14}C] Total Radioactivity in Feces,
Subjects 011 through 020
Percent of Dose per Collection Interval**



Fecal radioactivity could be lost through incomplete or missed collection. Since the blood and urine recovery indicate only trace amounts of radioactivity it is reasonable to conclude that colesevelam is not

absorbed.

B. Bioequivalence

Does the capsule formulation used in the NDA studies show comparable in vitro bile acid binding with the to-be-marketed tablet formulation?

An in vitro study was conducted to evaluate the bile acid binding capacity of the two formulations. Composite samples were prepared from tablets or capsules and testing was conducted as per the Interim Guidance for *in vitro* cholestyramine bioequivalence. Although some modifications were made to the protocol, these were found to be acceptable. The results of the comparison using Langmuir isotherms **without** acid pre-treatment (the pivotal bioequivalence measure) are shown in the table below and indicate that the binding capacity (k2) and affinity (k1) are comparable (±20%) for the two formulations.

DOSAGE FORM	K_1		
	GC	GCDC	TDC
Capsules	1.02	8.88	17.78
Tablets	2.00	8.68	15.62
DOSAGE FORM	K_2		
	GC	GCDC	TDC
Capsules	1.28	3.19	1.45
Tablets	1.05	3.23	1.43

The results of the comparison using Langmuir isotherms **with** acid pre-treatment are shown in the table below. The negative values of k1 maybe due to displacement of GC by TDC during the experiment. However, these results further support the similarity between the two dosage forms.

DOSAGE FORM	K_1		
	GC	GCDC	TDC
Capsules	-5.18	13.93	20.53
Tablets	-4.39	16.04	17.54
DOSAGE FORM	K_2		
	GC	GCDC	TDC
Capsules	0.63	3.00	1.38
Tablets	0.62	2.89	1.41

The capsule and tablet formulations are comparable in their bile acid binding.

II. Drug Interactions

Does colesevelam affect the bioavailability of other drugs?

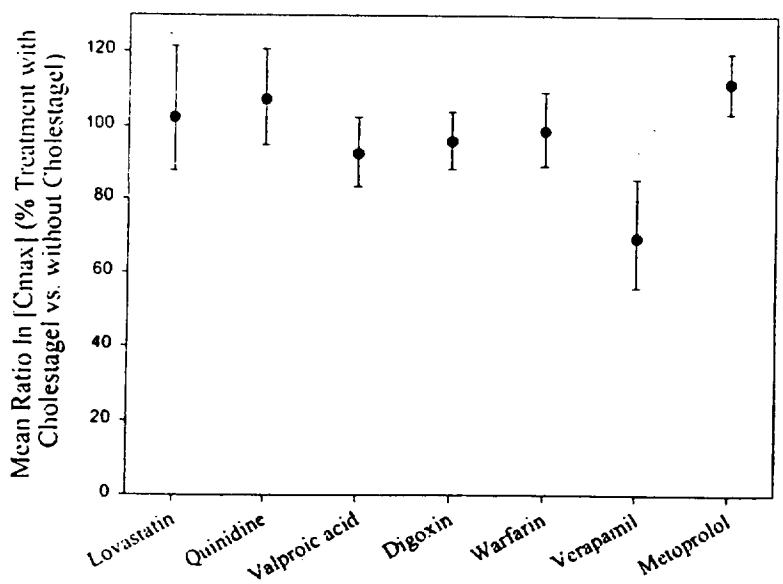
Seven drug interaction studies were conducted to explore the impact of colesevelam on the bioavailability of other drugs. The table below indicate the study, number of healthy subjects, and drugs/doses used.

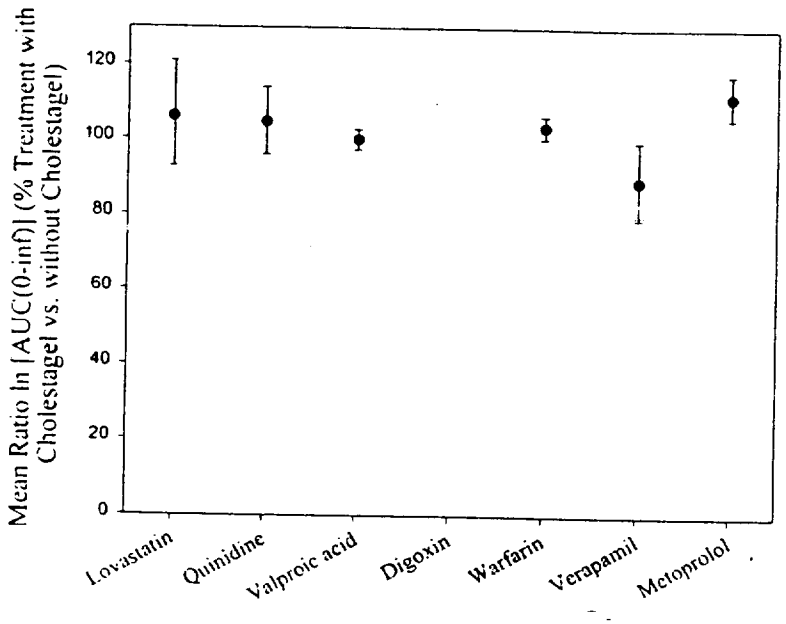
STUDY	DRUG	NUMBER ENROLLED	NUMBER COMPLETED
GTC-48-804	Quinidine	26	25
GTC-48-805	Valproic Acid	26	26
GTC-48-806	Digoxin	26	26
GTC-48-807	Warfarin	26	24
GTC-48-808	Verapamil	32	31
GTC-48-809	Metoprolol	36	33

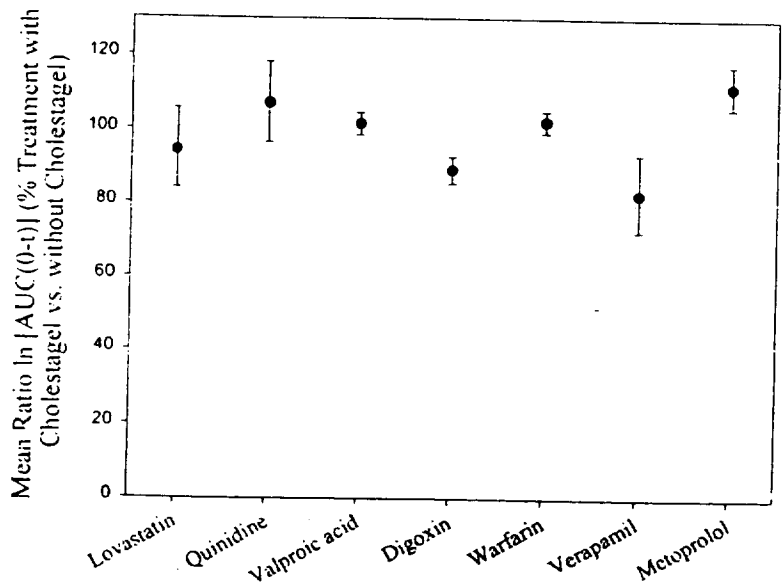
STUDY	DRUG	DOSE
GTC-48-804	Quinidine	324 mg
GTC-48-805	Valproic Acid	250 mg
GTC-48-806	Digoxin	0.25 mg
GTC-48-807	Warfarin	10 mg
GTC-48-808	Verapamil	240 mg
GTC-48-809	Metoprolol	100 mg

All studies were open-label, sequential-treatment design with an 8-15 day washout period. Subjects were fasted overnight before morning administration of study drug either with or without Cholestagel capsules (12x375mg); they then ate breakfast.

Results from these studies are summarized in the plots below.







Study results for lovastatin, quinidine, valproic acid, digoxin, warfarin, and metoprolol indicate that Cholestagel does not alter the bioavailability of these drugs.

For verapamil, administered as Calan SR, the Cmax and AUC decreased for the active parent verapamil as well as the active metabolite norverapamil (about 20% as active as parent), as shown in the table below.

Pharmacokinetic parameters	Verapamil		Norverapamil	
	90%CI	Point estimate	90%CI	Point estimate
Ln (Cmax)	**56.2**-85.6	**69.4**	**67.1**-88.3	**77**
Ln(AUC0-inf)	79.2-99.6	88.9	80.7-95.7	87.9
Ln(AUC0-t)	**72.5**-93.9	82.5	82.4-94.8	88.4

The sponsor proposes to label this as an 11% decrease in bioavailability. However, this reflects only the AUC0-t data; information about the Cmax should be included, too.

DISCUSSION:

A radiolabeled study indicates only trace amounts of radioactivity in blood and urine after administration of colesevelam. This demonstrates a lack of systemic absorption. Although fecal recovery of radioactivity was variable, this could be the result of missed or lost fecal sampling.

Colesevelam does not inhibit the absorption of lovastatin, quinidine, valproic acid, digoxin, warfarin, and metoprolol. Verapamil Cmax and to a lesser extent AUC are decreased when administered with Cholestagel but the clinical significance of this is unclear.

Labeling discussions are on-going with the sponsor.

LABELING COMMENTS (NOTE – these have already been conveyed to the sponsor):

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

1) Pharmacokinetics

[ ]

In 16 healthy volunteers, an average of 0.05% of a single ^{14}C-labeled colesevelam dose was excreted in the urine when given following 28 days of chronic dosing of 1.9 grams of colesevelam hydrochloride twice per day.

☞ Data as per the ^{14}C study.

2) Drug Interactions

was found to have no significant effect on the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. decreased the Cmax and AUC of sustained-release verapamil (Calan SR ®) by approximately 31% and 11%, respectively.

[ ]

☞ Specific data should be included in the label. The 11% decrease was only part of the data.

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ON ORIGINAL

Robert M. Shore, Pharm.D. /S/ 28-APR-00
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 13-APR-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ for Hae-Young Ahn 4/28/00

CC: NDA 21-141/N-000 (xref 21-176/N-000) (orig.,1 copy), HFD-510(Koch), HFD-870(Ahn, HuangS), CDR.

DFS Code: AP

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Appendix 1. Draft labeling

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Labeling

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Appendix 2. Study summaries

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Name of Sponsor/Company: GelTex Pharmaceuticals, Inc. **Name of Finished Product:** Cholestagel® **Name of Active Ingredient:** Colesevelam Hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of Study:	Absorption of ^{14}C-Colesevelam Hydrochloride in Normal Volunteers
Protocol Number:	GTC-48-803a
Investigator(s):	[redacted]
Study Site:	[redacted]
Publication (reference):	Not applicable
Study Period:	Date of first enrollment: February 01, 1999 Date last subject completed: March 10, 1999
Primary Objectives:	To assess the non-absorbability of colesevelam hydrochloride in normal volunteers
Methodology:	Single center, open-label, radiolabeled study

Number of Subjects (planned and analyzed):

	Male	Female	Total
Planned	20 normal volunteers		20
Enrolled	10	10	20
Discontinued	1	3	4
Completed	9	7	16

Diagnosis and Main Criteria for Inclusion:	Healthy normal volunteers, 18 years of age or older
Test product, dose and mode of administration, batch number:	5 x 375 mg Cholestagel® (colesevelam hydrochloride) capsules Lot No. EC76C, administered orally, b.i.d. x 28 outpatient and 4 inpatient days 6 x — mg [^{14}C]Cholestagel® (colesevelam hydrochloride) capsules, specific activity 200 µCi/g, Batch No. 98-776-42-16, administered orally x 1 inpatient dose
Duration of treatment:	Treatment with colesevelam hydrochloride for approximately 5 weeks
Reference product, dose and mode of administration, batch number:	Not applicable
Criteria for evaluation:	Volunteers must have completed screening assessments, treatment with colesevelam on Study Days –28 to –1, and Study Days 1 to 4, and all post-study assessments in order to be included in the radioactivity recovery analysis. All volunteers enrolled in the study were included in the safety analysis.

Name of Sponsor/Company: GelTex Pharmaceuticals, Inc. **Name of Finished Product:** Cholestagel® **Name of Active Ingredient:** Colesevelam Hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Statistical Methods:	Not applicable	
Safety Assessment:	Safety was to be assessed on the basis of changes in physical examinations, adverse events grouped by body system, and changes in safety laboratory values.	

SUMMARY – CONCLUSIONS

RADIOACTIVITY RECOVERY RESULTS:

An analysis of colesevelam hydrochloride equivalent concentrations in whole blood based on total radioactivity was conducted out to 96 hours post drug administration. In addition, an analysis of total radioactivity excreted out to 96 and 216 hours post drug administration was completed for urine and feces, respectively.

The mean maximum whole blood equivalent concentration (C_{max}) of colesevelam hydrochloride was 0.17 ± 0.10 µg equiv./g at 72 hours post-dose. This value equated to 0.04% of the administered dose circulating in the blood. The mean cumulative recovery of total radioactivity in urine through 96 hours was 0.05 ± 0.01 percent of dose. The mean cumulative recovery of total radioactivity in feces through 216 hours was 82.4 ± 16.1 percent of dose.

SAFETY RESULTS:

There were not any deaths or serious adverse events reported during this study. Of the 20 subjects enrolled in this study, 19 (95%) reported at least one adverse event. Of the 16 subjects who received non-radiolabeled and radiolabeled drug, 15 (93.8%) subjects reported at least one adverse event, and of the 4 subjects who received only non-radiolabeled drug, 4 (100%) reported at least one adverse event. Of the 71 adverse events that were reported, the relationship to study drug was not related for 40, remotely related for 7, possibly related for 19, and probably related for 5. Thirty-nine (39) were described as mild and 32 were described as moderate. Eight (8) subjects with 8 adverse events that were considered not related to the study drug required treatment with concomitant medication. Additionally, 1 of these 8 subjects also received Depo-Provera® for contraceptive purposes prior to the start of the study.

Name of Sponsor/Company: GelTex Pharmaceuticals, Inc. Name of Finished Product: Cholestagel® Name of Active Ingredient: Colesevelam Hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

CONCLUSION:

The trace amounts of radioactivity found in whole blood and urine are consistent with the non-absorbability of colesevelam hydrochloride, except for a small residual amount of soluble, low molecular weight unincorporated material. Given the negligible cumulative excretion amount observed in urine, a cumulative excretion in feces of 82.4 ± 16.1 % of dose is consistent with complete drug elimination through the gastro-intestinal system, with negligible absorption.

Cholestagel® (colesevelam hydrochloride, 3.8 g x 28 outpatient and 4 inpatient days, and [^{14}C]-colesevelam hydrochloride, 2.4 g x 1 inpatient dose) was safe and well tolerated by 19 of the 20 healthy, normal subjects enrolled in this study. One subject, Subject No. 004, had clinically significant changes in laboratory values which returned to normal or to a level that was <1.5 x normal upon exit.

Date of the Report: 28 June 1999

REVIEWER'S COMMENTS FOR STUDY 803:

1. If absorption was to have occurred some radioactivity should have been present in blood and/or urine. The low fecal recovery in a few subjects could be due to loss during sample collection.
2. Acceptable.

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REPORT SYNOPSIS

TITLE: A Drug Interaction Study To Evaluate The Effect Of Concomitant Administration Of CholestaGel® On The Pharmacokinetics Of Lovastatin In Healthy Male And Female Volunteers.

SPONSOR: GelTex Pharmaceuticals, Inc.
Waltham, MA 02154

STUDY SITE: [ ]

INVESTIGATOR: ———————

OBJECTIVES: The objective of this study was to assess the potential interaction of CholestaGel® and lovastatin when 1) lovastatin is administered with dinner, 2) both lovastatin and CholestaGel® are administered with dinner, and 3) CholestaGel® is administered with dinner and lovastatin is administered four hours later with a snack.

STUDY DESIGN: This study had a Phase I, single center, open label, three-period, crossover drug interaction design.

TREATMENTS:

A,B,C: Mevacor® (Lovastatin) 20 mg tablet
Merck & Company, Inc.
Lot No. D1941
Expiration date November, 1998

ADM1: CholestaGel® 400 mg capsule
Lot No. 630401
Expiration date not provided

Subjects randomized to Treatment A received a single oral dose of one 20 mg Mevacor® tablet followed by 180 mL water at zero hour, with the evening meal.

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ON ORIGINAL

Subjects randomized to Treatment B received a single oral dose of six 400 mg CholestaGel® capsules and one 20 mg Mevacor® tablet followed by 180 mL water at zero hour, with the evening meal.

Subjects randomized to Treatment C received a single oral dose of six 400 mg CholestaGel® capsules followed by 180 mL water at zero hour, with the evening meal and one 20 mg Mevacor® tablet followed by 180 mL water at four hours, with an evening snack.

PK MEASURES AND METHODS: The pharmacokinetics were assessed by measuring serial plasma lovastatin and hydroxyacid metabolite concentrations after administration of each formulation. The drug interaction between CholestaGel® and lovastatin administration was assessed by testing if the difference in mean response for AUC(0-t), AUC(0-inf), and Cmax for lovastatin administered in Treatment A differs by more than 25% from the respective mean values for lovastatin when administered as Treatment B and C.

RESULTS: Noncompartmental pharmacokinetic analyses were performed on plasma lovastatin and lovastatin hydroxyacid metabolite data. The statistical analysis results are summarized below.

Lovastatin Pharmacokinetic Parameters

Lovastatin Pharmacokinetic Parameters	Treatment A Arithmetic Mean (SD)	Treatment B Arithmetic Mean (SD)	Treatment C Arithmetic Mean (SD)
Cmax (ng/mL)	3.016 (2.545)	2.743 (1.508)	1.121 (0.5472)
AUC(0-t) (ng*hr/mL)	9.307 (5.239)	8.507 (4.254)	5.873 (2.662)
AUC(0-inf) (ng*hr/mL)	11.03 (6.325)	9.974 (5.366)	8.845 (4.624)
Tmax (hr)	1.18 (0.568)	1.14 (0.351)	2.37 (1.06)
Kel (1/hr)	0.1981 (0.0652)	0.2018 (0.0740)	0.1685 (0.0872)
T1/2el (hr)	3.840 (1.154)	3.934 (1.586)	5.323 (2.960)
LN(Cmax)	0.8650 (0.6911)	0.8823 (0.5246)	-0.003 (0.5021)
LN[AUC(0-t)]	2.096 (0.5264)	2.039 (0.4516)	1.668 (0.4724)
LN[AUC(0-inf)]	2.263 (0.5294)	2.186 (0.4727)	2.036 (0.6114)

Statistical Comparisons: Lovastatin

Treatment B Versus Treatment A			
Pharmacokinetic Parameters	Percentage Difference (%)	P Values B-0.75A < 0	P Values B-1.25A > 0
Cmax (ng/mL)	-8.88	0.9319	0.9916
AUC(0-t) (ng*hr/mL)	-8.54	0.9933	0.9999
AUC(0-inf) (ng*hr/mL)	0.54	0.9932	0.9670
Treatment C Versus Treatment A			
Pharmacokinetic Parameters	Percentage Difference (%)	P Values C-0.75A < 0	P Values C-1.25A > 0
Cmax (ng/mL)	-62.84	0.0005	1.000
AUC(0-t) (ng*hr/mL)	-37.01	0.0336	1.000
AUC(0-inf) (ng*hr/mL)	-35.17	0.2428	0.9994

Treatment A: 1 x 20 mg Mevacor® (Lovastatin) with evening meal
Treatment B: 1 x 20 mg Mevacor® (Lovastatin) with evening meal and 6 x 400 mg CholestaGel® capsules
Treatment C: 1 x 20 mg Mevacor® (Lovastatin) with evening snack four hours after evening meal and 6 x 400 mg CholestaGel® capsules

Lovastatin Hydroxyacid Metabolite Pharmacokinetic Parameters

Lovastatin Hydroxyacid Metabolite Pharmacokinetic Parameters	Treatment A Arithmetic Mean (SD)	Treatment B Arithmetic Mean (SD)	Treatment C Arithmetic Mean (SD)
Cmax (ng/mL)	1.499 (0.7552)	1.459 (0.6026)	2.414 (0.9479)
AUC(0-t) (ng*hr/mL)	9.417 (4.059)	8.706 (3.941)	14.14 (4.947)
AUC(0-inf) (ng*hr/mL)	10.78 (4.188)	10.06 (4.684)	15.73 (5.526)
Tmax (hr)	4.00 (2.26)	3.50 (2.84)	5.73 (0.984)
Kel (1/hr)	0.2917 (0.1107)	0.2069 (0.0917)	0.3214 (0.0837)
T1/2el (hr)	2.784 (1.286)	4.037 (1.813)	2.351 (0.8738)
LN(Cmax)	0.2856 (0.5036)	0.3013 (0.3932)	0.8060 (0.4088)
LN[AUC(0-t)]	2.155 (0.4320)	2.066 (0.4580)	2.587 (0.3728)
LN[AUC(0-inf)]	2.306 (0.3952)	2.212 (0.4459)	2.694 (0.3692)

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ON ORIGINAL

Statistical Comparisons: Lovastatin Hydroxyacid Metabolite

Treatment B Versus Treatment A			
Pharmacokinetic Parameters	Percentage Difference (%)	P Values B-0.75A < 0	P Values B-1.25A > 0
Cmax (ng/mL)	-2.67	0.9671	0.9648
AUC(0-t) (ng*hr/mL)	-7.53	0.9470	0.9896
AUC(0-inf) (ng*hr/mL)	-5.50	0.9328	0.9661
Treatment C Versus Treatment A			
Pharmacokinetic Parameters	Percentage Difference (%)	P Values C-0.75A < 0	P Values C-1.25A > 0
Cmax (ng/mL)	60.84	1.000	0.0105
AUC(0-t) (ng*hr/mL)	50.23	1.000	0.0351
AUC(0-inf) (ng*hr/mL)	45.72	1.000	0.0889

Treatment A: 1 x 20 mg Mevacor® (Lovastatin) with evening meal
Treatment B: 1 x 20 mg Mevacor® (Lovastatin) with evening meal and 6 x 400 mg CholestaGel® capsules
Treatment C: 1 x 20 mg Mevacor® (Lovastatin) with evening snack four hours after evening meal and 6 x 400 mg CholestaGel® capsules

CONCLUSION: The pharmacokinetic and statistical analyses indicated that CholestaGel® did not appear to affect the bioavailability of either lovastatin or lovastatin hydroxyacid metabolite when administered together with the evening meal. The mean values of the Cmax, AUC(0-t) and AUC(0-inf) for both lovastatin and lovastatin hydroxyacid metabolite for Treatment B were less than 9% different from Treatment A, and none of the p-values were statistically significant ($p > 0.05$).

The comparison of Treatment C to Treatment A demonstrated significantly reduced Cmax and AUC(0-t) for the inactive lovastatin and significantly increased Cmax and AUC(0-t) for the active lovastatin hydroxyacid metabolite. The effect of time of lovastatin administration and/or the composition of the meals likely explain these differences.

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 801:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

REPORT SYNOPSIS

TITLE: A Study to Determine the Effect of Colesevelam HCl (Cholestagel®) on Single Dose Quinidine Gluconate (Quinaglute Dura-Tabs®) Pharmacokinetics in Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02451

STUDY SITE: [ ]

INVESTIGATOR: _____

OBJECTIVES: The objective of this study was to determine the effect of a 4.5 g dose of colesevelam HCl (Cholestagel®) on single dose pharmacokinetics of quinidine gluconate in healthy subjects following a single, 324 mg dose of quinidine gluconate (Quinaglute Dura-Tabs®).

STUDY DESIGN: This was an open-label, sequential treatment study and was conducted in compliance with good clinical practice.

TREATMENTS:

A: Quinaglute Dura-Tabs® ER 324 mg tablets
Manufactured by Berlex Laboratories
Lot No. 8M00785
Expiration Date Sep 30 2000

All subjects received a single oral dose of one 324 mg Quinaglute Dura-Tabs® ER tablet taken with 240 mL of water on Days 1 and 8 of the study.

B: _____ Cholestagel® 375 mg capsules
Manufactured by GelTex Pharmaceuticals, Inc.
Lot No. EC78E
Expiration date not provided

All subjects received a single oral dose of twelve 375 mg Cholestagel® capsules on Day 8 of the study, co-administered with one 324 mg Quinaglute Dura-Tabs® tablet.

APPEARS THIS WAY
ON ORIGINAL

For pharmacokinetic analysis, all blood samples taken after 165 hours after day 1 were considered Treatment B.

PK MEASURES AND METHODS: The effect of Cholestagel® on the pharmacokinetics of quinidine was assessed by measuring serial plasma quinidine concentrations following a single dose administration of Quinaglute Dura-Tabs® alone (Day 1, Treatment A) and following its co-administration with 4.5 g of Cholestagel® (Day 8, Treatment B). Cholestagel® was considered to have no significant effect on the bioavailability of quinidine if the 90% confidence intervals for log-transformed (ratio B/A) Cmax, AUC(0-t), and AUC(0-inf) were within the range of ———— . The parameter values of Kel, T1/2el and Tmax were also compared between treatments.

RESULTS: The arithmetic means of the plasma quinidine pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Pharmacokinetic Parameters of Plasma Quinidine for Treatments A and B

	Plasma Quinidine					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(ug*hr/mL)	10.41	3.708	9.856	2.664		
AUC(0-t)(ug*hr/mL)	9.398	3.620	8.715	2.570		
Cmax(ug/mL)	0.68	0.25	0.64	0.19		
Kel(1/hr)	0.0742	0.0177	0.0703	0.0182		
LN(Cmax)	-0.4358	0.3318	-0.5044	0.3456	94.9-120.8	107.1
LN[AUC(0-inf)]	2.299	0.2847	2.254	0.2702	95.8-113.9	104.6
LN[AUC(0-t)]	2.189	0.3094	2.122	0.3104	96.8-118.1	107.0
T 1/2el(hr)	9.89	2.48	10.5	2.76		
Tmax(hr)	5.44	1.83	5.00	1.38		

Treatment B = 1 x 324 mg Quinaglute Dura-Tabs Co-administered with 12 x 375 mg Cholestagel Capsules: test
Treatment A = 1 x 324 mg Quinaglute Dura-Tabs: reference

CONCLUSION: The single dose pharmacokinetic and statistical analyses of quinidine plasma concentration data associated with the administration of one 324 mg Quinaglute Dura-Tabs® tablet alone or one 324 mg Quinaglute Dura-Tabs® tablet co-administered with 4.5 g of Cholestagel® have shown that Cholestagel® had no significant effect on the bioavailability of quinidine. The 90% confidence intervals for log-transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the range of ————

REVIEWER'S COMMENTS FOR STUDY 804:

1. Acceptable.

REPORT SYNOPSIS

TITLE: A Study To Determine The Effect Of Colesevelam HCL (Cholestagel®) On Single Dose Valproic Acid (Depakene®) Pharmacokinetics In Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02154

STUDY SITE: [ ]

INVESTIGATOR: ———————

OBJECTIVES: The objective of this study was to determine the effect of 4.5 g doses of colesevelam HCl (Cholestagel®) on single dose pharmacokinetics of valproic acid in healthy fasted subjects following a single, 250 mg dose of valproic acid (Depakene®).

STUDY DESIGN: This was an open-label, sequential treatment study and was conducted in compliance with good clinical practice.

TREATMENTS:

A: Valproic Acid 250 mg capsules (Depakene®)
Manufactured by Abbott
Lot No. 42200AW21
Expiration date 01 Jul 2001

All subjects received a single oral dose of one 250 mg valproic acid capsule taken with 240 mL of water on Days 1 and 8 of the study.

Admin 1: Cholestagel® 375 mg capsules
Manufactured by GelTex Pharmaceuticals, Inc.
Lot No. EC783
Expiration date not provided

All subjects received a single oral dose of twelve 375 mg Cholestagel® capsules on Day 8 of the study, co-administered with one 250 mg valproic acid capsule.

For pharmacokinetic analysis, all blood samples taken after 165 hours after day 1 were considered Treatment B.

PK MEASURES AND METHODS: The effect of Cholestagel® on the pharmacokinetics of valproic acid was assessed by measuring serial plasma valproic acid concentrations following a single dose administration of Depakene® alone (Day 1, Treatment A), and following its co-administration with 4.5 g of Cholestagel® (Day 8, Treatment B). Cholestagel® was considered to have no significant effect on the bioavailability of valproic acid if the 90% confidence intervals for log-transformed (ratio B/A) Cmax, AUC(0-t), and AUC(0-inf) were within the range of ——— The parameter values of Kel, T1/2el and Tmax were also compared between treatments.

RESULTS: The arithmetic means of the plasma valproic acid pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Pharmacokinetic Parameters of Plasma Valproic Acid for Treatments A and B

Pharmacokinetic Parameters	Plasma Valproic Acid ------- Treatment B Arithmetic Mean	SD	Treatment A Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(ug*hr/mL)	507.7	144.8	503.8	147.1		
AUC(0-t)(ug*hr/mL)	459.2	133.3	461.9	135.1		
Cmax(ug/mL)	27.13	7.96	28.76	6.37		
Kel(1/hr)	0.0466	0.0108	0.0464	0.0109		
LN(Cmax)	3.268	0.3037	3.336	0.2180	83.4-102.6	92.6
LN[AUC(0-inf)]	6.188	0.3066	6.182	0.2927	97.1-102.6	99.8
LN[AUC(0-t)]	6.109	0.3071	6.093	0.2994	98.6-104.6	101.5
T 1/2el(hr)	15.9	3.43	15.8	3.78		
Tmax(hr)	1.40	1.64	1.06	1.12		

Treatment B = 1 x 250 mg Depakene Capsule with 12 x 375 mg Cholestagel Capsules: test
Treatment A = 1 x 250 mg Depakene Capsule: reference

CONCLUSION: The single dose pharmacokinetic and statistical analyses of valproic acid plasma concentration data associated with the administration of one 250 mg Depakene® capsule alone, or one 250 mg Depakene® capsule co-administered with 4.5 g of Cholestagel® have shown that Cholestagel® had no significant effect on the bioavailability of valproic acid. The 90% confidence intervals for log-transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the range of ———

REVIEWER'S COMMENTS FOR STUDY 805:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

REPORT SYNOPSIS

TITLE: A Study to Determine the Effect of Colesevelam HCl (CholestaGel®) on Single Dose Digoxin (Lanoxin®) Pharmacokinetics in Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02451

STUDY SITE: [ ]

INVESTIGATOR: _____

OBJECTIVES: The objective of this study was to determine the effect of a 4.5 g dose of colesevelam HCl (CholestaGel®) on single dose pharmacokinetics of digoxin in healthy subjects following a single, 0.25 mg dose of digoxin (Lanoxin®).

STUDY DESIGN: This was an open-label, sequential treatment study and was conducted in compliance with good clinical practice.

TREATMENTS:

A: Lanoxin® 0.250 mg tablets
Manufactured by Glaxo Wellcome
Lot No. 8P03008
Expiration date 30 Nov 2000

All subjects received a single oral dose of one 250 µg Lanoxin® tablet taken with 240 mL of water on Days 1 and 8 of the study.

Admin 1: CholestaGel® 375 mg capsules
Manufactured by GelTex Pharmaceuticals, Inc.
Lot No. EC78E
Expiration date not provided

All subjects received a single oral dose of twelve 375 mg CholestaGel® capsules on Day 8 of the study, co-administered with one 250 µg Lanoxin® capsule.

For pharmacokinetic analysis, blood samples taken after 335 hours after day 1 were considered Treatment B.

PK MEASURES AND METHODS: The effect of CholestaGel® on the pharmacokinetics of digoxin was assessed by measuring serial plasma digoxin concentrations following a single dose administration of Lanoxin® alone (Day 1, Treatment A), and following its co-administration with 4.5 g of CholestaGel® (Day 15, Treatment B). CholestaGel® was considered to have no significant effect on the bioavailability of digoxin if the 90% confidence intervals for log-transformed (Ratio B/A) Cmax and AUC(0-24) were within the range of ———%. The parameter values of Tmax were also compared between treatments.

RESULTS: The arithmetic means of the plasma digoxin pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Plasma Digoxin Pharmacokinetic Parameters for Treatments B and A

	Plasma Digoxin					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-24)(ng*hr/mL)	5.8447	1.6098	6.5239	1.5068		
Cmax(ng/mL)	0.883	0.299	0.909	0.240		
LN(Cmax)	-0.1696	0.2944	-0.1275	0.2567	88.4-104.0	95.9
LN[AUC(0-24)]	1.733	0.2557	1.848	0.2444	85.5- 92.9	89.1
Tmax(hr)	0.583	0.0718	0.849	0.429		

Treatment B = 1 X 0.25 mg Lanoxin Tablet Co-administered with 12 X 375 mg CholestaGel Capsules: test
Treatment A = 1 X 0.25 mg Lanoxin Tablet: reference

APPEARS THIS WAY
ON ORIGINAL

CONCLUSION: The single dose pharmacokinetic and statistical analyses of digoxin plasma concentration data associated with the administration of one 0.25 mg Lanoxin® tablet alone, or one 0.25 mg Lanoxin® tablet co-administered with 4.5 g of CholestaGel® have shown that CholestaGel® had no significant effect on the extent or the rate of availability of digoxin. The 90% confidence intervals for log-transformed Cmax and AUC(0-24) were both within the —— range.

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 806:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

REPORT SYNOPSIS

TITLE: A Study to Determine the Effect of Colesevelam HCl (Cholestagel®) on Single Dose Warfarin Sodium (Coumadin®) Pharmacokinetics in Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02451

STUDY SITE: [redacted]

INVESTIGATOR: [redacted]

OBJECTIVES: The objective of this study was to determine the effect of a 4.5 g dose of colesevelam HCl (Cholestagel®) on single dose pharmacokinetics of warfarin sodium in healthy subjects following a single, 10 mg dose of warfarin sodium (Coumadin®).

STUDY DESIGN: This was an open-label, sequential treatment study and was conducted in compliance with good clinical practice.

TREATMENTS: A: Coumadin® 10 mg tablets
Manufactured by [redacted]
Lot No. EMD213A
Expiration date 30 Apr 2001

All subjects received a single oral dose of one 10 mg Coumadin® tablet taken with 240 mL of water on Day 1 of study.

Admin 1: Cholestagel® 375 mg capsules
Manufactured by GelTex Pharmaceuticals, Inc.
Lot No. EC78E
Expiration date not provided

All subjects received a single oral dose of twelve 375 mg Cholestagel® capsules on Day 15 of the study, co-administered with one 10 mg Coumadin® tablet.

For pharmacokinetic analysis, all blood samples taken after 335 hours after Day 1 were considered Treatment B.

PK MEASURES AND METHODS: The effect of Cholestagel® on the pharmacokinetics of warfarin was assessed by measuring serial plasma warfarin concentrations following a single dose administration of Coumadin® alone (Day 1, Treatment A), and following its co-administration with 4.5 g of Cholestagel® (Day 15, Treatment B). Cholestagel® was considered to have no significant effect on the bioavailability of warfarin if the 90% confidence intervals for log-transformed (Ratio B/A) Cmax, AUC(0-t), and AUC(0-inf) were within the range of ——— The parameter values of Kel, T1/2el, and Tmax were also compared between treatments.

RESULTS: The arithmetic means of the plasma warfarin pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Plasma Warfarin Pharmacokinetic Parameters for Treatments B and A

	Plasma Warfarin					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(ng*hr/mL)	50397	13658	49391	13071		
AUC(0-t)(ng*hr/mL)	45810	11516	45453	11536		
Cmax(ng/mL)	1182.19	319.87	1176.46	250.53		
Kel(1/hr)	0.0142	0.00289	0.0147	0.00240		
LN(Cmax)	7.040	0.2741	7.050	0.2046	89.3-109.3	98.8
LN[AUC(0-inf)]	10.79	0.2856	10.77	0.2807	100.3-106.4	103.3
LN[AUC(0-t)]	10.70	0.2705	10.69	0.2720	99.3-105.1	102.2
T 1/2el(hr)	50.6	9.47	48.5	8.46		
Tmax(hr)	1.22	1.73	1.74	2.86		

Treatment B = 1 X 10 mg Coumadin Tablet Co-administered with 12 X 375 mg Cholestagel Capsules: test
Treatment A = 1 X 10 mg Coumadin Tablet: reference

CONCLUSION: The single dose pharmacokinetic and statistical analyses of warfarin plasma concentration data associated with the administration of one 10 mg Coumadin® tablet alone, or one 10 mg Coumadin® tablet co-administered with 4.5 g of Cholestagel® have shown that Cholestagel® had no significant effect on the bioavailability of warfarin. The 90% confidence intervals for log-transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the range of ———

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 807:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

REPORT SYNOPSIS

TITLE: A Study To Determine The Effect Of Colesevelam HCl (CholestaGel®) On Single Dose Verapamil HCl (Calan SR®) Pharmacokinetics In Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02154

STUDY SITE: [ ]

INVESTIGATOR: _____

OBJECTIVES: The objective of this study was to determine the effect of a 4.5 g dose of colesevelam HCl (CholestaGel®) on single dose pharmacokinetics of verapamil HCl in healthy subjects following a single, 240 mg dose of verapamil HCl (Calan SR®).

STUDY DESIGN: This was an open-label, sequential treatment study and was conducted in compliance with good clinical practice.

TREATMENTS:

A: Calan SR® 240 mg caplet
Manufactured by G.D. Searle & Co.
Lot No. 7S051
Expiration date 30 Jun 2000

All subjects received a single oral dose of one 240 mg Calan SR® caplet taken with 240 mL of water on Days 1 and 8 of the study.

Admin 1: CholestaGel® 375 mg capsule
Manufactured by GelTex Pharmaceuticals, Inc.
Lot No. EC78E
Expiration date not provided

All subjects received a single oral dose of twelve 375 mg CholestaGel® capsules on Day 8 of the study, co-administered with one 240 mg Calan SR® caplet.

For pharmacokinetic analysis, blood samples taken after 165 hours after day 1 were considered Treatment B.

PK MEASURES AND METHODS: The effect of CholestaGel® on the pharmacokinetics of verapamil and norverapamil were assessed by measuring serial plasma verapamil and norverapamil concentrations following a single dose administration of Calan SR® alone (Day 1, Treatment A), and following its co-administration with 4.5 g of CholestaGel® (Day 8, Treatment B). CholestaGel® was considered to have no significant effect on the bioavailability of verapamil and norverapamil if the 90% confidence intervals for log-transformed (ratio B/A) Cmax, AUC(0-t), and AUC(0-inf) were within the range of ——— The parameter values of Kel, T1/2el, and Tmax were also compared between treatments. In addition, the pharmacokinetic parameters for combined verapamil and norverapamil concentrations were reported.

RESULTS: The arithmetic means of the plasma verapamil pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Plasma Verapamil Pharmacokinetic Parameters for Treatments B and A

	Plasma Verapamil					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(ng*hr/mL)	1133	403.1	1325	380.5		
AUC(0-t)(ng*hr/mL)	928.4	392.6	1166	463.5		
Cmax(ng/mL)	71.366	51.017	106.036	71.803		
Kel(1/hr)	0.0921	0.0236	0.0962	0.0222		
LN(Cmax)	4.067	0.6217	4.437	0.7209	56.2- 85.6	69.4
LN[AUC(0-inf)]	6.961	0.4198	7.147	0.2998	79.2- 99.6	88.9
LN[AUC(0-t)]	6.743	0.4428	6.949	0.5471	72.5- 93.9	82.5
T 1/2el(hr)	7.91	1.66	7.58	1.74		
Tmax(hr)	11.3	7.44	9.00	4.24		

Treatment B = 1 X 240 mg Calan SR Caplet Co-administered with 12 X 375 mg CholestaGel Capsules: test
Treatment A = 1 X 240 mg Calan SR Caplet: reference

APPEARS THIS WAY
ON ORIGINAL

The arithmetic means of the plasma norverapamil pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Plasma Norverapamil Pharmacokinetic Parameters for Treatments B and A

	Plasma Norverapamil					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(ng*hr/mL)	1561	388.6	1911	435.9		
AUC(0-t)(ng*hr/mL)	1500	345.0	1738	455.4		
Cmax(ng/mL)	70.076	25.910	95.173	42.090		
Kel(1/hr)	0.0697	0.0178	0.0760	0.0189		
LN(Cmax)	4.192	0.3357	4.459	0.4570	67.1- 88.3	77.0
LN[AUC(0-inf)]	7.323	0.2551	7.528	0.2467	80.7- 95.7	87.9
LN[AUC(0-t)]	7.286	0.2400	7.421	0.3015	82.4- 94.8	88.4
T 1/2el(hr)	10.6	2.64	9.69	2.50		
Tmax(hr)	14.4	7.19	11.5	5.48		

Treatment B = 1 X 240 mg Calan SR Caplet Co-administered with 12 X 375 mg CholestaGel Capsules: test
Treatment A = 1 X 240 mg Calan SR Caplet: reference

The arithmetic means of the combined plasma verapamil and norverapamil pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Combined Plasma Verapamil and Norverapamil Pharmacokinetic Parameters for Treatments B and A

	Combined Plasma Verapamil and Norverapamil					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-inf)(nmol*hr/mL)	5.730	1.780	7.054	1.786		
AUC(0-t)(nmol*hr/mL)	5.505	1.585	6.663	1.921		
Cmax(nmol/mL)	0.305	0.148	0.439	0.244		
Kel(1/hr)	0.0796	0.0192	0.0878	0.0223		
LN(Cmax)	-1.284	0.4454	-0.9702	0.5690	62.2- 86.8	73.4
LN[AUC(0-inf)]	1.699	0.3167	1.920	0.2727	78.1- 90.8	84.2
LN[AUC(0-t)]	1.666	0.2939	1.830	0.3491	79.1- 92.9	85.8
T 1/2el(hr)	9.19	2.13	8.42	2.20		
Tmax(hr)	12.2	7.11	10.0	4.42		

Treatment B = 1 X 240 mg Calan SR Caplet Co-administered with 12 X 375 mg CholestaGel Capsules: test
Treatment A = 1 X 240 mg Calan SR Caplet: reference

CONCLUSION: The single dose pharmacokinetic and statistical analyses of verapamil and norverapamil plasma concentration data associated with the administration of one 240 mg Calan SR® caplet alone, or one 240 mg Calan SR® caplet co-administered with 4.5 g of Cholestagel® have shown that Cholestagel® had significant effect on the bioavailability of both verapamil and norverapamil. For verapamil, the lower boundaries of the 90% confidence intervals for log-transformed Cmax, AUC(0-t), and AUC(0-inf) were all below the — lower limit of the —— range, indicating both impaired rate and extent of verapamil absorption in the presence of Cholestagel®. For norverapamil, comparison of the concentration profiles between Day 1 and Day 8 administrations showed also lower mean peak concentration in the presence of Cholestagel®. Lower bounderies of the 90% confidence limit for log-transformed Cmax, AUC(0-t) and AUC(0-inf) were within the —— range.

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 808:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

REPORT SYNOPSIS

TITLE: A Study to Determine the Effect of Colesevelam HCl (Cholestagel®) on Single Dose Metoprolol Tartrate (Lopressor®) Pharmacokinetics in Healthy Subjects

SPONSOR: GelTex Pharmaceuticals, Inc.
Nine Fourth Avenue
Waltham, MA 02451

STUDY SITE: [ ]

INVESTIGATOR: _____

OBJECTIVES: The objective of this study is to determine the effect of a 4.5 g dose of colesevelam HCl (Cholestagel®) on single dose pharmacokinetics of metoprolol in healthy subjects following a single 100 mg dose of metoprolol tartrate (Lopressor®).

STUDY DESIGN: This study had an open-label, sequential treatment, design.

TREATMENTS: A: Lopressor® (100 mg metoprolol tartrate USP) tablets
Manufactured by Novartis
Lot No. 1T235705
Expiration date 01 Sep 2003

All subjects received a single dose of one 100 mg metoprolol tartrate USP tablet taken with 240mL of room temperature tap water on Days 1 and 8 of the study.

ADM1: Cholestagel 4.5g HFC capsules
Manufactured by GelTex
Lot No. EC78E
Expiration date not provided

APPEARS THIS WAY
ON ORIGINAL

For Period 2, Day 8, all subjects received twelve 375 mg capsules taken with 240 mL of room temperature tap water co-administered with one 100 mg Lopressor® tablet. For pharmacokinetic analysis, Period 2 (Day 8), was re-assigned as Treatment B.

PK MEASURES AND METHODS: The effect of Cholestagel® on the pharmacokinetics of metoprolol was assessed by measuring serial plasma metoprolol concentrations following a single dose administration of Lopressor® alone (Day 1, Treatment A), and following its co-administration with 4.5 g of Cholestagel® (Day 8, Treatment B). Cholestagel® was considered to have no significant effect on the bioavailability of metoprolol if the 90% confidence intervals for log-transformed (ratio B/A) Cmax, AUC(0-t), and AUC(0-inf) were within the range of ——— The parameter values of Kel, T1/2el, and Tmax were also compared between treatments.

RESULTS: The arithmetic means of the plasma metoprolol pharmacokinetic parameters and the statistical comparisons for Treatments A and B are summarized in the following table:

Summary of the Pharmacokinetic Parameters of Plasma Metoprolol for Treatments B and A

	Plasma Metoprolol					
	Treatment B		Treatment A			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/mL)	156.47	82.49	139.97	69.00		
Tmax(hr)	1.38	0.648	1.95	0.980		
AUC(0-t)(ng*hr/mL)	946.7	536.4	852.8	498.1		
AUC(0-inf)(ng*hr/mL)	987.8	559.0	890.3	518.9		
T 1/2el(hr)	3.29	0.939	3.01	1.02		
Kel(1/hr)	0.225	0.0560	0.252	0.0677		
LN(Cmax)	4.932	0.5027	4.824	0.4999	103.6-119.9	111.5
LN[AUC(0-t)]	6.691	0.5904	6.581	0.5984	106.0-117.5	111.6
LN[AUC(0-inf)]	6.736	0.5848	6.627	0.5923	105.8-117.6	111.5

Treatment B = 1 x 100 mg Lopressor Tablet Co-administered with 12 x 375 mg Cholestagel Capsules: test
Treatment A = 1 x 100 mg Lopressor Tablet: reference

APPEARS THIS WAY
ON ORIGINAL

CONCLUSION: The single dose pharmacokinetic and statistical analyses of metoprolol plasma concentration data associated with the administration of one 100 mg Lopressor® tablet alone, or one 100 mg Lopressor® tablet co-administered with 4.5 g of Cholestagel® have shown that Cholestagel® had no significant effect on the rate and extent of metoprolol absorption. The 90% confidence intervals for the comparison of Treatments B to A for log-transformed Cmax, AUC(0-t), and AUC(0-inf) for metoprolol were all within the acceptable —— range.

APPEARS THIS WAY
ON ORIGINAL

REVIEWER'S COMMENTS FOR STUDY 809:

1. Acceptable.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL