

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-141 and 21-176

ADMINISTRATIVE DOCUMENTS

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

Date of Review: 2/22/00
NDA#: 21-141
Name of Drug: Welchol®
(colesevelam tablets, capsules)
NDA Holder: GelTex Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) on February 4, 2000, to review the proposed proprietary drug name, Welchol® in regard to potential name confusion with existing proprietary/generic drug names.

Cholestagel® was the original name submitted by the firm. This name was initially submitted to the Labeling and Nomenclature Committee (LNC) on 9/22/99 and found to be unacceptable on 11/10/99 due to significant potential for confusion with existing product, colestipol (Colestid®) currently marketed.

OPDRA's review on 12/20/1999, concurred with LNC's recommendation that the proposed proprietary name, Cholestagel® was not acceptable.

The firm resubmitted a proposed proprietary name, Welchol®, on 2/3/00 to replace Cholestagel® and asked for an expedited decision by 3/1/00.

PRODUCT INFORMATION

Welchol® (colesevelam hydrochloride) is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. It may be administered alone or in combination with an HMG-CoA reductase inhibitor ("statin"). The firm is seeking approval on both 375 mg capsules and 625 mg tablets, _____
_____ The usual starting dose for monotherapy is 6 tablets once a day or 3 tablets taken twice a day with meals,

which may be increased to 7 tablets a day. If Welchol® is added to HMG-CoA RI (reductase inhibitor) therapy, the recommended starting dose is ~ tablets once a day taken with a meal or ~ tablets twice a day with meals. A statin may also be added to Welchol® therapy, with dose of statin titrated to response.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Welchol® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (update monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online, Decision Support System (DSS), Establishment Evaluation System, and LNC database. An expert panel discussion was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process.

A. EXPERT PANEL DISCUSSION:

The expert panel consists of members of OPDRA medication error safety evaluator staff and a representative from the Division of Drug Marketing, Advertising and Communication.

The panel discussion was conducted on 2/14/00. There were no problems found with other similar proprietary drug product names. However, there was some concern expressed on the use of "Wel" in the name.

B. STUDY CONDUCTED BY OPDRA

Methodology:

This study involved 92 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Welchol® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An OPDRA staff member wrote three outpatient prescriptions, each consisting of a known drug product and a prescription for Welchol®. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient and inpatient

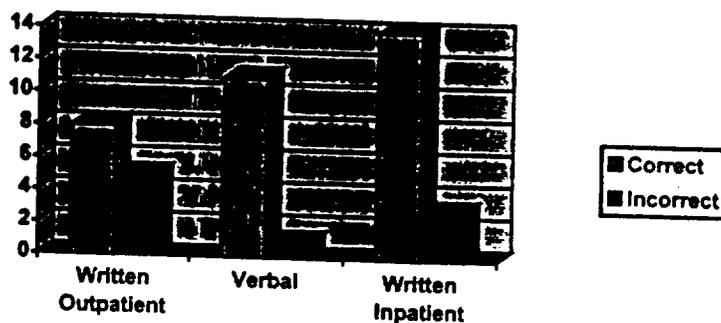
prescriptions were sent to 31 participants each for review. In addition, one pharmacist student recorded the outpatient orders on voice mail. The voice mail messages were then sent to 30 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We recognize that our sample size is small and the study is designed to increase the likelihood of detecting failures.

**APPEARS THIS WAY
ON ORIGINAL**

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Samples</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	31	13 (42%)	8	5
Verbal	30	12 (40%)	11	1
Written Inpatient	31	17 (55%)	14	3
Total	92	42 (47%)	33	9



Seventy-nine percent of the participants responded with the correct name Welchol®. The incorrect written and verbal responses are as follows in Table II :

Table II

	<u>Incorrectly Interpreted</u>
<u>Written Outpatient</u>	Uteldrol
	Melchol
	Medrol (3)*
<u>Written Inpatient</u>	Welehol
	Welibol
	Welihol
<u>Verbal</u>	<u>Phonetic Variable Response</u>
	Valco

* Currently marketed proprietary name

C. CONTAINER LABEL, CARTON AND INSERT LABELING:

Container label and carton labeling are not available for review.

D. CONCLUSIONS:

Results of the verbal and written analysis studies show 33 participants interpreted proprietary name Welchol® correctly. There were nine incorrect interpretations for both written prescriptions and verbal orders. In addition, the inaccurate interpretations of the proposed name did overlap with an existing approved drug product, Medrol®. That was not what we predicted in the expert panel discussion, and is a significant finding in a study with a small sample size. Welchol® and Medrol® have similar character lengths (Welchol has 7 and Medrol has 6). Welchol® starts with "W" and Medrol® with "M" and both end with "ol". Both look similar in written prescriptions. However, Welchol® comes as one strength of 625 mg tablet. Medrol® comes with 5 different strengths tablet (2 mg, 4 mg, 8 mg, 16 mg and 32 mg and 4 mg Dospak). The usual dosage for Medrol® is individualized from 4 to 48 mg per day until response is noted while Welchol® daily dose is 6 tablets (623 mg) once a day or 3 tablets twice a day. Though there is no overlapping strength nor dosing administration between these two products, the potential safety risk of error is significant since Medrol® and Welchol® are very similar when written (see actual written Rx below). Moreover, outpatient prescriptions for Medrol® Dospak are often written without a strength (4mg) and thus the risk is higher for an error to occur.

*Medrol
Dospak
Sig: As directed*

*Welchol
1 month
Sig: As directed*

When examining the clinical consequences of an error between these two products, two possibilities exist:

1. A prescription for Welchol® misinterpreted for Medrol® would have significant clinical implications resulting in patient complications due to fluid and electrolyte disturbances, osteoporosis, and hypertension.
2. A prescription for Medrol® misinterpreted for Welchol® could result in a persistent transaminase elevation.

III. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name Welchol®.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

/S/ 2/28/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

C.C.

NDA 21-141

Office File

HFD-510; Margaret Simoneau, Project Manager, DMEDP

HFD-510; John Jenkins, M.D., Acting Director, DMEDP

HFD-510; Lanh Green, Safety Evaluator, DMEDP

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Deputy Director, OPDRA (electronic copy)

HFD-002; Murray Lumpkin, Acting Director, OPDRA (electronic copy)

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 2/4/00	DUE DATE: 3/1/00	OPDRA CONSULT #: 00-0044
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TO :
John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Margaret Simoneau, Project Manager, DMEDP
HFD-510

PRODUCT NAME: Welchol® (colesevelam tablets, capsules) NDA #: 21-141	MANUFACTURER: GelTex Pharmaceuticals, Inc.
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Safety Evaluator: Peter Tam, R.Ph.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of the proprietary name Welchol®.

*per Dr. Atchiff request
Team on 3/1/00
3:15 PM c. De...
/S/*

/S/

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Jan 1 2-28-2000

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: December 20, 1999

DUE DATE: December 31, 1999

OPDRA CONSULT #: 99-081

TO: John Jenkins, MD
Acting Director, Division of Metabolic and Endocrine Drug Products (HFD-510)

PRODUCT NAME: CholestageTM
(colesevelam tablets, capsules)

MANUFACTURER: GeTex Pharmaceuticals, Inc.

NDA #: 21-141

CASE REPORT NUMBER(S): Not applicable.

SUMMARY:

In response to a consult from the Division of Metabolic and Endocrine Drug Products, OPDRA conducted a review of the proposed proprietary name "CholestageTM" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:

From a safety perspective, we do not recommend the use of the name "CholestageTM".

/S/

12/23/99

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

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/S/

12/27/99

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**APPEARS THIS WAY
ON ORIGINAL**

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 20, 1999
NDA NUMBER: 21-141
NAME OF DRUG: Cholestagel™ (colesevelam capsules, tablets)
NDA HOLDER: GelTex Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename Cholestagel™.

Cholestagel™ was initially submitted to the Labeling and Nomenclature Committee (LNC) on September 22, 1999 and found to be unacceptable on November 10, 1999. LNC concluded that two existing product names, cholestyramine and Colestid, had low potential for confusion and colestipol had medium potential for confusion with Cholestagel.

Cholestagel™ (colesevelam hydrochloride) is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. It may be administered alone or in combination with an HMG-CoA reductase inhibitor ("statin"). The manufacturer is seeking approval of both 375-mg capsules and 625-mg tablets, _____

_____ The usual starting dose for monotherapy is 6 tablets once a day or 3 tablets taken twice a day with meals, which may be increased to 7 tablets per day. If Cholestagel is added to HMG-CoA RI therapy, the recommended starting dose is _____ tablets once a day taken with a meal or _____ tablets twice a day with meals. A statin may also be added to Cholestagel therapy, with dose of the statin titrated to response.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.),

sound alike or look alike to Cholestagel™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An internal focus group discussion was conducted to review all findings from the searches.

One existing product name, colestipol (hydrochloride), was considered by OPDRA to have significant potential for confusion with Cholestagel. Colestipol HCl (Colestid™) is a lipid-lowering drug, supplied as 1 gram tablets and powder for oral suspension. The usual starting dose of Colestid™ tablets is two tablets (2 g) once or twice daily, with dose increases as needed up to 16 tablets (16 grams) per day. Some concern was also voiced regarding the word ending "gel", which gives the impression that this product is a topical gel dosage form.

B. Handwritten and verbal analysis of proposed names

A study was conducted within FDA employing health care professionals to evaluate potential errors in handwritten and verbal communications of the name Cholestagel. This exercise was conducted in an attempt to simulate usual clinical practice settings. One of the following prescriptions was communicated per each FDA reviewer. Each reviewer was then requested to provide an interpretation of this prescription via email.

HANDWRITTEN PRESCRIPTION (n=45)	VERBAL PRESCRIPTION (n=47)
Cholestagel 625mg, #180, 3 bid with meals, 2 refills.	Cholestagel 625mg, take 3 tablets bid with meals, dispense 180 with 2 refills

Results of this exercise are provided in Tables 2 and 3 (see page 4). The majority of respondents to the written survey interpreted the name correctly (22 of 23 responses, 96%). The verbal survey respondents provided misspelled variations of the drug name but these responses generally were phonetic variations of the name. However, one respondent to the verbal surveys independently noted the potential for confusion with colestipol. Another noted the similarity between the dietary supplement Cholestin, a 600mg capsule. The usual dose of Cholestin is two capsules twice a day with food.

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Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

ⁱⁱ American Drug Index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, Updated October 1999, Facts and Comparisons, St. Louis, MO.

^{iv} Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

III. RECOMMENDATIONS

OPDRA does not recommend use of the proprietary name CholestageTM.

OPDRA would appreciate feedback on the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

**APPEARS THIS WAY
ON ORIGINAL**

/S/

12/23/97

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-141
HFD-510; Division Files/Margaret Simoneau, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Lanh Green, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

TO (Division/Office): *HFD-H00 OPDRA*
 FROM: *HFD-510 METABOLIC AND ENDOCRINE DRUG PRODUCTS*

DATE: *1/4/99* IND NO. NDA NO. *21-141* TYPE OF DOCUMENT DATE OF DOCUMENT

N. OF DRUG: *CHOLESTIARL (colesevelam HCl)* PRIORITY CONSIDERATION CLASSIFICATION OF DRUG DESIRED COMPLETION DATE: *1/1/00*

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
 PROGRESS REPORT
 NEW CORRESPONDENCE
 DRUG ADVERTISING
 ADVERSE REACTION REPORT
 MANUFACTURING CHANGE/ADDITION
 MEETING PLANNED BY

PRE-NDA MEETING
 END OF PHASE II MEETING
 RESUBMISSION
 SAFETY/EFFICACY
 PAPER NDA
 CONTROL SUPPLEMENT

RESPONSE TO DEFICIENCY LETTER
 FINAL PRINTED LABELING
 LABELING REVISION
 ORIGINAL NEW CORRESPONDENCE
 FORMULATIVE REVIEW
 OTHER (SPECIFY BELOW):
TRADENAME REVIEW

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH STATISTICAL APPLICATION BRANCH

TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

AVAILABILITY STUDIES
 PHASE IV STUDIES

DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAJVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the enclosed Submission, (Enclosed copy of proposed label)
If there are any questions please contact:
Chemist - MARTIN Haber 301-827-6388
Project Manager - MARGARET SIMONOV 76418

SIGNATURE OF REQUESTER: */S/* METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER: */S/* SIGNATURE OF DELIVERER

Electronic Mail Message

Date: 9/22/99 5:01:42 PM
From: Martin Haber
To: Dan Boring (HABERM)
Cc: Margaret Simoneau (BORINGD)
Subject: Cholestagel Tradename, NDA 21-141 (SIMONEAUM)

Please find attached a request for trademark review. I sent identical hard copy by Holy envelope.

Martin

**APPEARS THIS WAY
ON ORIGINAL**

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, HFD-530, 9201 Corporate Blvd, Room
N461

From: Division of Metabolic and Endocrine Drug Products/ HFD-510
Attention: Martin Haber, Chemist
6388 Phone: (301) 827-

Date: September 22, 1999

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Cholestagel **NDA #:** 21-141

Company Name: GelTex Pharmaceuticals, Inc.

Established name, including dosage form: Colesevelam HCl

Dosage form: 625 mg tablet and 375 mg capsule

Other trademarks by the same firm for companion products: Renagel, a phosphate binder

Indications for Use (may be a summary if proposed statement is lengthy):

Hypercholesterolemia

Initial comments from the submitter (concerns, observations, etc.):

The drug substance is an insoluble allylamine polymer crosslinked with _____ and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide in the hydrochloride form. It is a non-absorbed bile acid binder. Both tablets and capsules are proposed as dosage forms.

filename:

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Exclusivity Checklist

NDA: 21-141				
Trade Name: Welchol capsules				
Generic Name: colesevelam hydrochloride				
Applicant Name: GelTex Pharmaceuticals, Inc.				
Division: HFD-510				
Project Manager: William C. Koch				
Approval Date: May 17, 2000				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?		Five		
IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.				
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	X	No	
	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.				
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	X
	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.				
	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
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If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO **DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
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1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

	Yes		No	
--	-----	--	----	--

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

	Yes		No	
--	-----	--	----	--

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?			
Investigation #1	Yes	No	
Investigation #2	Yes	No	
Investigation #3	Yes	No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1			
Investigation #2			
Investigation #3			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.			
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			

Exclusivity Checklist

NDA: 21-176			
Trade Name: Welchol tablets			
Generic Name: colestevlam hydrochloride			
Applicant Name: GelTex Pharmaceuticals, Inc.			
Division: HFD-510			
Project Manager: William C. Koch			
Approval Date: May 17, 2000			
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?			
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.			
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/>	No
b. Is it an effectiveness supplement?	Yes		No <input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	<input checked="" type="checkbox"/>	No
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.			
Explanation:			
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:			
Explanation:			
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No
If the answer to (d) is "yes," how many years of exclusivity did the applicant request? Five			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.			
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No <input checked="" type="checkbox"/>
If yes, NDA #			
Drug Name:			
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.			
3. Is this drug product or indication a DESI upgrade?	Yes		No <input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).			

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
--	-----	--	----	--

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
---	-----	--	----	--

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
--	-----	--	----	--

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
---	-----	--	----	--

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?			
Investigation #1	Yes	No	
Investigation #2	Yes	No	
Investigation #3	Yes	No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1			
Investigation #2			
Investigation #3			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.			
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	

1 M
 / S /
Signature of PM

 04/18/00
Date:

 / S /
Signature of Division or Office Director

 5/11/00
Date:

cc:
Original NDA
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

**APPEARS THIS WAY
ON ORIGINAL**

March 30, 2000

PATENT INFORMATION

Patent Number: 5,624,963
Date of Expiration: April 29, 2014
Type of Patent: Method of Use Patent and Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,624,963 covers the composition and method of use of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

March 30, 2000

PATENT INFORMATION

Patent Number: 5,679,717
Date of Expiration: April 29, 2014
Type of Patent: Method of Use Patent and Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,679,717 covers the composition and method of use of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

Confidential

March 30, 2000

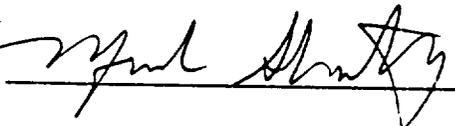
PATENT INFORMATION

Patent Number: 5,693,675
Date of Expiration: December 2, 2014
Type of Patent: Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,693,675 covers the composition of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 
Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

Confidential

March 30, 2000

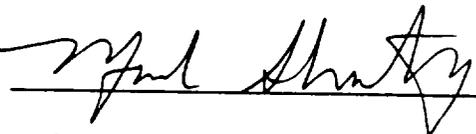
PATENT INFORMATION

Patent Number: 5,607,669
Date of Expiration: June 10, 2014
Type of Patent: Method of Use
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,607,669 covers the method of use of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

Confidential

March 30, 2000

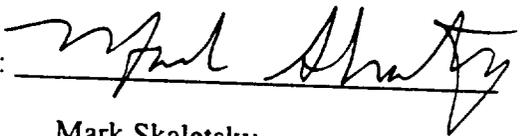
PATENT INFORMATION

Patent Number: 5,917,007
Date of Expiration: April 29, 2014
Type of Patent: Method of Use Patent and Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,917,007 covers the composition and method of use of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

Confidential

March 30, 2000

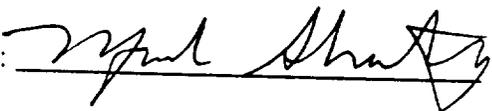
PATENT INFORMATION

Patent Number: 5,919,832
Date of Expiration: June 10, 2014
Type of Patent: Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,919,832 covers the composition of colesevelam hydrochloride as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

March 30, 2000

CLAIM OF EXCLUSIVITY BASED ON 21 CFR 314.108(b)(2)

GelTex Pharmaceuticals, Inc. ("GelTex") is claiming exclusivity for colesevelam hydrochloride. The exclusivity is claimed based on 21 CFR 314.108(b)(2). To the best of GelTex's knowledge or belief, a drug has not previously been approved under Section 505(b) of the Federal Food, Drug and Cosmetic Act containing any active moiety in colesevelam hydrochloride.

GELTEX PHARMACEUTICALS, INC

By: _____



Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

Confidential

July 30, 1999

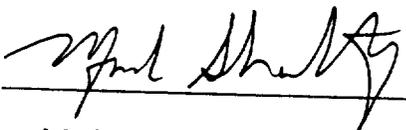
PATENT INFORMATION

Patent Number: 5,624,963
Date of Expiration: April 29, 2014
Type of Patent: Method of Use Patent and Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,624,963 covers the composition and method of use of Cholestagel® as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

July 30, 1999

PATENT INFORMATION

Patent Number: 5,679,717
Date of Expiration: April 29, 2014
Type of Patent: Method of Use Patent and Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,679,717 covers the composition and method of use of Cholestage[®] as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: _____



Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

July 30, 1999

PATENT INFORMATION

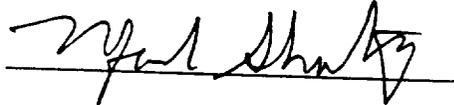
Patent Number: 5,693,675
Date of Expiration: December 2, 2014
Type of Patent: Drug Substance Patent
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,693,675 covers the composition of Cholestagel[®] as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By:



Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

July 30, 1999

PATENT INFORMATION

Patent Number: 5,607,669
Date of Expiration: June 10, 2014
Type of Patent: Method of Use
Patent Owner: GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts

Original Declaration:

The undersigned declares that Patent No. 5,607,669 covers the method of use of Cholestagel® as a bile acid sequestrant. This product is the subject of this application for which approval is being sought.

GELTEX PHARMACEUTICALS, INC

By: 

Mark Skaletsky
President and CEO

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21141</u>	Trade Name:	<u>Welchol</u>
Supplement Number:		Generic Name:	<u>COLESEVELAM HCL</u>
Supplement Type:		Dosage Form:	<u>Capsule; Oral</u>
Regulatory Action:	<u>PN</u>	Proposed Indication:	<u>Adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy	<u>Inadequate for ALL pediatric age groups</u>
Formulation Status	
Studies Needed	<u>STUDIES needed. Applicant has COMMITTED to doing them</u>
Study Status	<u>Protocols are under discussion. Comment attached</u>

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

March 17, 1999 - applicant requested deferment of pediatric studies until after approval of drug in adults

April 10, 2000 - refer to comment above.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, WILLIAM C. KOCH

<u>IS/</u>	<u>04/19/00</u>
Signature	Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21176</u>	Trade Name:	<u>WELCHOL 625MG TABLET</u>
Supplement Number:		Generic Name:	<u>COLESEVELAM HCL</u>
Supplement Type:		Dosage Form:	<u>Tablet; Oral</u>
Regulatory Action:	<u>PN</u>	Proposed Indication:	<u>Adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hyperchloesterolemia</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy	<u>Inadequate for ALL pediatric age groups</u>
Formulation Status	<u>NO NEW FORMULATION is needed</u>
Studies Needed	<u>STUDIES needed. Applicant in NEGOTIATIONS with FDA</u>
Study Status	<u>Protocols are under discussion. Comment attached</u>

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

March 17, 1999 - applicant requested deferment of pediatric studies until after approval of drug in adults.

April 10, 2000 - refer to comment above.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, WILLIAM C. KOCH

Signature IS/

Date 04/19/00

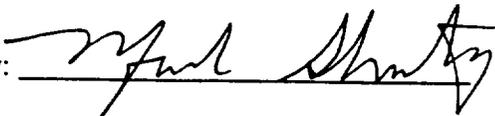
16. DEBARMENT CERTIFICATION

March 30, 2000

CERTIFICATION PURSUANT TO 21 U.S.C. 306(k)(1)

GelTex Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with these applications.

GELTEX PHARMACEUTICALS, INC.

By: 
Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

16. DEBARMENT CERTIFICATION

July 30, 1999

CERTIFICATION PURSUANT TO 21 U.S.C. 306(k)(1)

GelTex Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

GELTEX PHARMACEUTICALS, INC.

By: 

Mark Skaletsky
President and CEO

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

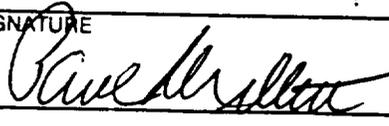
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached list.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Paul Mellett		TITLE Chief Financial Officer	
FIRM/ORGANIZATION GelTex Pharmaceuticals, Inc.			
SIGNATURE 		DATE 7/28/99	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

19. CLINICAL INVESTIGATOR FINANCIAL DISCLOSURE

As required in 21 CFR 54.4(a)(1), attached for certain clinical investigators [as defined in 21 CFR 54.2(d)], is a completed Form FDA 3454, attesting to the absence of financial interests and arrangements described in 21 CFR 54.4(a)(3).

For the remaining — clinical investigators [as defined in 21 CFR 54.2(d)], attached is a certification attesting to the sponsor's due diligence in attempting to obtain the information, and the reason why such information was not obtained.

**APPEARS THIS WAY
ON ORIGINAL**

Confidential

WITHHOLD 5 PAGE (S)

July 30, 1999

CERTIFICATION PURSUANT TO 21 CFR 54.4(c)

GelTex Pharmaceuticals, Inc. hereby certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but has been unable to do so for the — clinical investigators listed below.

The reason financial disclosure information has not been received from these investigators is because to date they have failed to respond to written requests for this information, including a letter sent by certified mail, return receipt requested.

GELTEX PHARMACEUTICALS, INC.

By: Paul Mellett

Paul Mellett
Chief Financial Officer

Investigators from whom completed financial disclosure forms have not been received

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Confidential



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB - 4 2000

Jonathan L. Isaacsohn, M.D.
Medical Research Services, 2nd Floor
2350 Auburn Avenue
Cincinnati, OH 45217

Dear Dr. Isaacsohn:

On January 5th and 6th, 2000, Mr. Joseph X. Kaufman, representing the Food and Drug Administration (Agency), inspected your conduct as the investigator of record of your clinical study (Protocol #GTC-48-301) of the investigational drug CholestaGel[®] Capsules that you conducted for GelTex Pharmaceuticals, Inc. From our evaluation of the inspection report and the documents submitted with that report, we conclude that you conducted your study in compliance with Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Mr. Kaufman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

**APPEARS THIS WAY
ON ORIGINAL**



Donald B. Hunninghake, M.D.
University of Minnesota
Heart Disease Prevention Clinic
Box 192, Room 151
Variety Club Heart & Research Center
401 E. River Parkway
Minneapolis, Minnesota 55455

Food and Drug Administration
Rockville MD 20857

FEB 29 1999

BEST POSSIBLE COPY

Dear Dr. Hunninghake:

Between November 15 and November 18, 1999, Ms. Sharon L. Matson, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (GTC-48-301) of CholestaGel® (colesevelam hydrochloride) that you conducted for GelTex Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

Ms. Matson presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of: (a) the inspection report; (b) your oral responses during the inspection; and (c) your letter of December 2, 1999, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. Specifically, you failed to document the informed consent of at least one subject using a current, IRB-approved informed consent form.

Your letter of December 2, 1999, responds to the items listed on the Form FDA 483. We accept your explanations and acknowledge your assurance that corrective actions will be taken to prevent similar problems in your current and future studies. Your letter has been added to your file. If information is requested from your file in accord with the Freedom of Information Act, our response will include the related correspondence in your file.

We appreciate the cooperation shown Ms. Matson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy (HFD-45)
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

**APPEARS THIS WAY
ON ORIGINAL**

Food and Drug Administration
Rockville MD 20857

FEB - 4 2000

William S. Mullican, M.D.
1401 Professional Boulevard
Medisphere Medical Research Center
Evansville, IN 47714

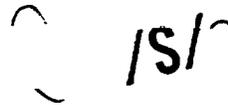
Dear Dr. Mullican:

Between October 25 and October 27, 1999, Mr. Douglas W. Gronski, representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (protocol #GTC-48-301a) of the investigational drug CholestaGel™ (colesevelam hydrochloride), that you conducted for GelTex Pharmaceuticals, Inc. From our evaluation of the inspection report and the documents submitted with that report, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We appreciate the cooperation shown Mr. Gronski during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



David A. Lepad, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

**APPEARS THIS WAY
ON ORIGINAL**



Memorandum

Date May 25, 2000

From Steven R. Koepke, ^{/S/}
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA 21-141, 21-176
Welchol Tablets and Capsules (colesevelam hydrochloride)
GelTex Pharmaceuticals

GelTex Pharmaceuticals originally submitted these applications as a single entity. The applications were split into two since CDER under current policy does not allow different dosage forms (tablets and capsules) in the same application.

Welchol Tablets and capsules are composed primarily of an ion exchange polymer resin that binds bile acids for elimination. The controls and specifications for these applications although unusual for standard drug substances are typical of those required of cross-linked polymeric materials. Activity is measured directly by an in-vitro bile acid. The major impurities are related to starting materials and incomplete polymerization (_____ primarily) or are _____

_____ There are adequate specifications in place to monitor these.

[_____]

Overall CMC recommendation: The only outstanding CMC issues as of CMC review #2 were the outstanding inspection request and the environmental assessment consult. Both are now satisfactory as of CMC review #3 (May 23, 2000) and the application is recommended for approval from CMC.

Environmental assessment: The environmental assessment has resulted in a Finding of No Significant Impact. Adequate 4/25/00

Facility Inspections: Acceptable 5/11/00

Tradename: Acceptable 4/13/00 OPDRA

Labeling: Acceptable from CMC

**APPEARS THIS WAY
ON ORIGINAL**

**Executive CAC
March 21, 2000**

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Glenna Fitzgerald, Ph.D., HFD-120, Alternate Member
Ronald Steigerwalt, Ph.D., Team Leader
Gemma Kuijpers, Ph.D., Presenting Reviewer

Author of Draft: Gemma Kuijpers

The following information reflects a brief summary of the Committee discussion and its conclusions. Detailed study information can be found in the individual reviews.

NDA # 21,141
Drug Name: Colesevelam Hydrochloride (Welchol)
Category: Bile acid sequestrant
Sponsor: Geltex Pharmaceuticals, Inc., MA

1. Rat Carcinogenicity Study**104-week study**

Doses: 0, 0, 0.4, 1.2, 2.4 g/kg/day

Discussed were mortality data, body weight data, dose levels and tumor findings. Histopathology examination was carried out of all animals in groups 1 and 2 (controls) and group 5 (high dose group), and of preterminally sacrificed or dead animals in groups 3 and 4 (low and mid dose groups). All macroscopic abnormalities and all organs/tissues were evaluated by histopathological examination.

Colesevelam was associated with an increase in survival in high dose male rats, and a slight decrease in body weight in mid dose and high dose male rats. In the male rats, survival was 18% and 32% in control groups 1 and 2, respectively, and 58% in the high dose group. There was a statistically significant linear trend in survival distribution among the dose groups in the male rat. In the mid and high dose groups, body weight was 97% and 93%, respectively, of control group 2 in male rats, at 104 weeks. There was no effect on body weight in female rats.

Test article concentrations in the diet of the high dose groups reached 5% for males in week 46-47 and 4% for females in week 62 of the study. 80% and 90% of this diet percentage level was reached for males in weeks 10 and 20, and for females in weeks 6 and 14.

There was a significant dose-tumor positive linear trend for benign pancreatic acinar cell adenoma in male rats ($p=0.002$). In males, there was an increased incidence of thyroid C-cell adenoma as compared to control groups 1 and 2, and in females there was an increased incidence of thyroid C-cell adenoma as compared to control group 2 but not control group 1. There was also an increased incidence of pancreatic acinar cell hyperplasia and thyroid C-cell hyperplasia in mid and high dose males, both as compared to control 1 as well as control 2. Thyroid C-cell hyperplasia was not increased in females.

The Committee considered the dose levels adequate as the dietary concentrations had reached at least 85% of the maximum by study week 20. The question was raised whether the statistical analysis of tumor incidence was carried out with the data for the two control groups pooled, and it was suggested to do the analysis with only the data from control group 2. The Committee was concerned about the pancreatic findings (tumors, nodules and hyperplasia) in the males, and the thyroid C-cell adenoma in both sexes. The Committee was further concerned about a possible increased incidence of combined organ schwannomas, and an increased incidence of pancreatic islet cell carcinoma in the mid dose females (0/60 in control groups, and 3 out of 21 in mid dose group). It was suggested to ask the Sponsor to analyze the remaining low and mid dose animals. A question was also raised about the nature of the non-neoplastic lung granulomas with increased incidence in high dose males. The Committee also noted that the compound and/or some of its degradants had positive reactions in the CHO chromosomal aberration assay and asserted to not neglect these findings since they have not been shown to be irreproducible.

2. Mouse Carcinogenicity Study**104-week study****Doses: 0, 0, 0.3, 1.0, 3.0 mg/kg/day**

Discussed were mortality data, body weight data, dose levels and tumor findings. Histopathology examination was carried out of all animals in all groups and of all organs/tissues.

Colesevelam had no significant effect on mortality. Body weight was decreased in the high dose males and females at the end of the study. Another drug-related adverse effect appeared to be a decrease in the serum vitamin E levels in mid and high dose animals.

Test article concentrations in the diet of the high dose groups reached 2.1% for males in week 24 and 1.7% for females in week 23 of the study. 90% of this diet percentage level was reached for males in week 7, and for females in week 18.

There were no significant increases in the incidence of any tumor type in male or female mice.

The Committee judged that on the basis of the trends in body weight the doses used in this study were adequate. There was no concern about the tumorigenicity of the test compound in mice.

Conclusions:

Rat study: In a 104-week rat carcinogenicity study with colesevelam hydrochloride there was a statistically significant increase in the incidence of pancreatic acinar cell adenoma in male rats. There also appeared to be an increased incidence of thyroid C-cell tumor incidence in male and female animals. Additional statistical analysis was recommended to come to a more comprehensive conclusion on the thyroid tumor findings.

Mouse study: In a 104-week mouse carcinogenicity study with colesevelam hydrochloride there appeared to be no effects on tumor incidence in any organ in either male or female mice.

ISI
4/08/00
Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-510
/G. Kuijpers, HFD-510
/R. Steigerwalt, HFD-510
/R. Hedin, HFD-510
/A. Seifried, HFD-024

APPEARS THIS WAY
ON ORIGINAL