CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-141 and 21-176

CORRESPONDENCE

Filing Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date: 15-SEP-99
From: Robert M. Shore, Pharm.D.
Through: Hae-Young Ahn, Ph.D., Team Leader
To: Margaret Simoneau, CSO
Re: CholestaGel® (colesevelam HCl)
NDA 21-141/N-000 375 mg capsule
NDA 21-176/N-000 625 mg tablet
Geltex Pharmaceuticals, Inc.

SYNOPSIS:

NOTE: The submission for CholestaGel has been designated with two NDA numbers: 21-141/N-000 for the 375 mg capsule, and 21-176/N-000 for the 625 mg tablet. All data have been submitted to NDA 21-141/N-000 but all memos/reviews will cross-reference 21-176/N-000 for completeness.

CholestaGel (colesevelam HCl) is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their absorption. Cholestagel, administered alone or in combination with an HMG-CoA
reductase inhibitor, is proposed to be indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. For monotherapy, the recommended starting dose of Cholestagel is 6 tablets (3.75 gm) taken once per day or 3 tablets (1.875 gm) twice a day, with meals. The Cholestagel dose can be increased to 7 tablets (4.375 gm), depending upon the desired therapeutic effect. For combination therapy, if an HMG-CoA reductase inhibitor is added to Cholestagel therapy, the lowest effective starting dose of the HMG-CoA reductase inhibitor should be used and titrated to the desired therapeutic effect. If Cholestagel is added to HMG-CoA reductase inhibitor therapy, the recommended starting dose is – tablets ———)) taken once per day with a meal, or – tablets ——— twice a day with meals. The Cholestagel dose can be increased to – tablets ——— depending upon the desired therapeutic effect.

9 *in vivo* studies will be reviewed by DPE2 (Table 3-4.6): GTC-37-801 (drug interaction with lovastatin), GTC-48-802 (PD of bile acid excretion), GTC-48-803 (^{14}C ADME study), and GTC-48-804/5/6/7/8/9 (drug interactions studies). In addition, an *in vitro* bioequivalence study, based on the cholestyramine interim Guidance, was conducted to compare capsule and tablet formulations, since all clinical data was generated with capsules ———

At the time of filing of this NDA CholestaGel is not marketed in any other country.

According to the submission, colesevelam will be synthesized by [redacted] Capsules contain 375 mg colesevelam HCl, [redacted] Mg stearate in a white, opaque, hard gel capsule manufactured by [redacted] There have been a few changes to the capsule formulation through the development of CholestaGel.

The tablet formulation is: colesevelam HCl 625 mg, [redacted], microcrystalline cellulose [redacted] Mg stearate [redacted] silicon dioxide [redacted] The tablet will also be manufactured by [redacted] There is only one tablet formulation.

Assay validation data is included in study reports. This submission is electronic and paper.

The proposed commercial lot size is [redacted] tablets (section 4, page 56)

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has evaluated NDA 21-141/N-000 dated 30-JUL-99 for filing (there is no formal submission for NDA 21-176/N-000). Based on this review, DPE-2 has determined that the application is fileable. 'Comments to the Sponsor' should be forwarded to the sponsor.

COMMENTS TO THE SPONSOR:

1. As per the 'Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs', page 16, the sponsor should provide proposed draft labeling in a word processing format (The FDA standard is currently Word).

2. The release specs for CholestaGel include bile acid binding and disintegration. The actual data used to set the proposed specs could not be located in the submission. If they are included, the sponsor should indicate where they are; if not included, the sponsor should submit these data for evaluation.

3. A ^{14}C-labeled colesevelam ADME study in humans is referred to as study GTC-48-803 and GTC-37-803. The sponsor should clarify if this is the same study or if two studies were done.

4. It is indicated that the lots used in the *in vitro* bioequivalence study are: caps – EC75M, EC76M, EC78M; and tablets – EJ54M, EK12MB, UPM9901. The production size and formulation of most these lots could not be located in the submission. If this information is included, the sponsor should indicate where it is; if not included, the sponsor should submit this information.

CC: NDA 21-141/N-000(orig., 1 copy), NDA 21-176/N-000 (orig., 1 copy), HFD-510(Orloff, Shen, Simoneau, Wu, Haber, Steigerwalt, Kuijpers), HFD-870(Ahn, ChenME), CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

Table 3.4-6: Investigational Formulas

MANUFACTURER	CLINICAL STUDY NO.	DESCRIPTION	DRUG SUBSTANCE LOT(S)	DRUG PRODUCT LOT(S)	MG COLESEVELAM HYDROCHLORIDE %DRUG SUBSTANCE
[redacted]	GTC-37-203	A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Lovastatin Alone and in Combination in Patients with Primary Hypercholesterolemia	TKFC403-1499 TKFC404-1500	037416	375 mg 100% drug substance
[redacted]	GTC-37-801	A Drug Interaction Study to Evaluate the Effect of Concomitant Administration of Cholestagel on the Pharmacokinetics of Lovastatin in Healthy Male and Female Volunteers	TKFC401-1497 TKFC402-1498	106376	375 mg 100% drug substance

MANUFACTURER	CLINICAL STUDY NO.	DESCRIPTION	DRUG SUBSTANCE LOT(S)	DRUG PRODUCT LOT(S)	MG COLESEVELAM HYDROCHLORIDE %DRUG SUBSTANCE
[redacted]	GTC-48-204	A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Simvastatin Alone and in Combination in Patients with Primary Hypercholesterolemia	TMAC012-1865 TMAC013-1866	EC76D	375 mg 99% drug substance
[redacted]	GTC-48-205	A Randomized, Double-Blind, Placebo-Controlled Trial of Cholestagel and Atorvastatin Alone and in Combination in Patients with Primary Hypercholesterolemia	TMAC012-1865 TMAC013-1866	EC76D	375 mg 99% drug substance
[redacted]	GTC-48-301	A Randomized, Double-Blind Trial of Cholestagel versus Placebo in Patients with Primary Hypercholesterolemia	TLMC004-1839 TLMC005-1840 TLMC006-1842 TLMC007-1843	EC75M	375 mg 99% drug substance
[redacted]	GTC-48-302	A Randomized, Double-Blind, Placebo-Controlled Trial of Once-Per-Day versus Split Dosing of Cholestagel in Patients with Primary Hypercholesterolemia	TMAC012-1865 TMAC013-1866	EC76C	375 mg 99% drug substance
[redacted]	GTC-48-802	A Pharmacodynamic Study of the Effects of Cholestagel on Fecal Bile Acid Excretion	TMAC012-1865 TMAC013-1866	EC76C FD-159/S	375 mg 99% drug substance
[redacted] [redacted]	GTC-48-803	Absorption of ^{14}C-Cholestagel in Normal Volunteers	TMAC012-1865 TMAC013-1866 98-776-41-09	EC76C 98-776-42-16	375 mg 99% drug substance 375 mg 100% drug substance
[redacted]	GTC-48-804	A Study to Determine the Effect of Cholestagel® on Single Dose Quinidine Gluconate (Quinaglute Dura-Tabs®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance

MANUFACTURER	CLINICAL STUDY NO.	DESCRIPTION	DRUG SUBSTANCE LOT(S)	DRUG PRODUCT LOT(S)	MG COLESEVELAM HYDROCHLORIDE %DRUG SUBSTANCE
[redacted]	GTC-48-805	A Study to Determine the Effect of Cholestagel® on Single Dose Valproic Acid (Depakene®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance
[redacted]	GTC-48-806	A Study to Determine the Effect of Cholestagel® on Single Dose Digoxin (Lanoxin®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance
[redacted]	GTC-48-807	A Study to Determine the Effect of Cholestagel® on Single Dose Warfarin (Coumadin®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance
[redacted]	GTC-48-808	A Study to Determine the Effect of Cholestagel® on Single Dose Verapamil HCl (Calan SR®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance
[redacted]	GTC-48-809	A Study to Determine the Effect of Cholestagel® on Single Dose Metopolol (Lopressor®) Pharmacokinetics in Healthy Subjects	TMAC015-1868 TMAC014-1867	EC78E	375 mg 99% drug substance
[redacted]	GTC-44-201	An Open-Label, Fixed Dose, Safety Trial of Cholestagel® Tablets in Normal Volunteers	TMAC018-1871	UPM9901	625 mg 70% drug substance

APPEARS THIS WAY
ON ORIGINAL

Proposed Draft Labeling

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 9 PAGE (S)

Draft

Labeling

MEMORANDUM
May 15, 2000

TO: John K, Jenkins, M.D.
Leah Ripper
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-141
NDA 21-176 (Colesevelam HCL)

I have reviewed the action package and concur with the conclusions of the Pharmacology/Toxicology Reviewer (Dr. Gemma Kuijpers) and the Pharmacology/Toxicology Team Leader (Dr. Ronald W. Steigerwalt) concerning both the approvability of the NDAs and the product labeling (with one exception: see below). The single issue of potential genotoxicity of the drug substance was resolved and no further comment is needed.

In the section "Carcinogenesis, Mutagenesis, Impairment of Fertility", the following should be added as a third paragraph:

"Colesevelam ——— did not impair fertility in rats at doses up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg)."

In the section "PREGNANCY", in the first sentence, ——— ' should be omitted, as it is redundant with addition of the statement concerning impairment of fertility in the previous section of the label.

/S/

Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology

WITHHOLD 1 PAGE (S)

Draft

Labeling

4/3/00 Bill - To "Safety Update" via Athin Pkg

GelTex PHARMACEUTICALS, INC.

DUPLICATE

[redacted]

50

March 29, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Colesevelam hydrochloride
Amendment 007
Safety Update Report

Dear Sir/Madam:

Reference is made to the NDAs cited above for colesevelam hydrochloride, submitted July 30, 1999. As requested by Ms. Margaret Simoneau in a telephone conversation with Dean Alger on March 28, 2000, the purpose of this submission is to provide a Safety Update Report.

Please note that there is no new safety information to report for colesevelam hydrochloride at this time. There have been no ongoing or new clinical studies conducted with the drug since the submission was prepared. The Integrated Summary of Safety and the Risk-Benefit Discussion remain unchanged from the original submission.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
GelTex Pharmaceuticals, Inc.	March 29, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(781) 290-5888	(781) 434-3603
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
153 Second Avenue Waltham, MA 02451	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-141/21-176

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Colesevelam hydrochloride	Cholestagel® (to be replaced)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl] trimethylammonium chloride and N-allyldecylamine, hydrochloride (IUPAC)	GT31-104HB

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet and Capsule	625 mg (Tablet) 375 mg (Capsule)	Oral

(PROPOSED) INDICATION(S) FOR USE: Cholestagel, administered alone or in combination with HMG-CoA reductase inhibitors, is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet and exercise.

APPLICATION INFORMATION

APPLICATION TYPE (check one) CFR 314.94)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Safety Update Report

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(See attachment)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

(See attachment)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify) Clinical Investigator Financial Disclosure (Form FDA 3454)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Martha J. Carter.	Martha J. Carter Vice President, Regulatory Affairs	29 March 2000.

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
153 Second Avenue Waltham, MA 02451	(781) 434-3443

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DDHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

RECORD OF TELEPHONE CONVERSATION OR MEETING	DATE: 04/13/00 Time: 1000 hrs Location: PKLWN#14B04 68
FDA Attendees: W. Koch **Objectives:** Discuss acceptability of Submitted proprietary name, Welchol. **Discussion:** Division assessed March 27, 2000 submission. **Conclusion(s):** Division finds the Welchol Name acceptable. /S/ 04/13/00 William C. Koch, R.Ph. Date Regulatory Project Manager	**Telecon initiated by:** FDA **NDA:** 21-141 & 21-176 **Product name:** (colesevelam HCl) **Firm name:** GelTex Pharma **Name and title of person with whom conversation was held:** Dean Alger, Director, Regulatory Affairs **Telephone:** (781) 434-3421

Cc: Original NDA 's 21-176 & 21-141
Division File

Filename: _____

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM
May 15, 2000

TO: John K. Jenkins, M.D.
Leah Ripper
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-141
NDA 21-176 (Colesevelam HCL)

I have reviewed the action package and concur with the conclusions of the Pharmacology/Toxicology Reviewer (Dr. Gemma Kuijpers) and the Pharmacology/Toxicology Team Leader (Dr. Ronald W. Steigerwalt) concerning both the approvability of the NDAs and the product labeling (with one exception: see below). The single issue of potential genotoxicity of the drug substance was resolved and no further comment is needed.

In the section "Carcinogenesis, Mutagenesis, Impairment of Fertility", the following should be added as a third paragraph:

"Colesevelam ——— did not impair fertility in rats at doses up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg)."

In the section "PREGNANCY", in the first sentence, " ——— ." should be omitted, as it is redundant with addition of the statement concerning impairment of fertility in the previous section of the label.

/S/
Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1 PAGE (S)

Draft

Labeling

WITHHOLD 6 PAGE (S)

Draft

Labeling

Electronic Mail Message

Date: 4/27/00 2:28:55 PM
From: Nancy Sager (SAGERN)
To: William C. Koch (KOCHW)
Subject: EA 21-141 &21-176

The EA has been reviewed and it is acceptable. I will return the original review and FONSI through the mail. An EA amendment dated 4/25 will be submitted to the division. I don't need a copy of it because they sent me a desk copy.

Nancy

APPEARS THIS WAY
ON ORIGINAL

GelTex PHARMACEUTICALS, INC.

ORIGINAL

NEW CORRESP

NV

March 23, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 21-176
Colesevelam hydrochloride
Amendment 005
Response to March 14, 2000 Facsimile
Revised Environmental Assessment

Dear Sir/Madam:

Reference is made to the NDA cited above for Cholestagel® (colesevelam hydrochloride), and to the Agency's facsimile of March 14, 2000 containing additional comments on the environmental assessment in section 4.4.

The purpose of this submission is to respond to your comments. For ease of review, the Agency's requests/comments are repeated in ***bold italics***, followed by our responses. Also included with this submission is a revised environmental assessment (EA) in **Attachment 1**. The revisions to the EA are indicated in highlighted text.

General comment: Environmental Assessments (EAs) are considered public documents and are available once an application is approved. You may wish to obtain copies of recently approved EAs to guide you in the preparation of your EAs in the future.

The following deficiencies in the environmental assessment that was submitted on February 4, 2000 should be corrected and a revised EA submitted. The deficiency from the first review is listed followed by the recommended revision.

1. ***4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).***

   The information you provided in the February 4, 2000 response is adequate, however, you need to incorporate it into the EA document.

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

Please see section 4.4.1.6 (page 10) of the attached EA for this revision.

2. ***4.4.1.7.2 (deficiency a): A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included.***

   a. ***Solubility-Water: The response cross references a section of the NDA for this information. This needs to be summarized and included in the EA. Only a brief description of the test method (e.g., quantity, temperature, method (e.g., under/over saturation method)) used to determine the solubility in water needs to be provided in section 4.4.1.7.2.1 of the EA.***

Please see section 4.4.1.7.2.1 (page 23) of the attached EA for this information.

   b. ***Dissociation constant: The information is adequate but needs to be included in section 4.4.1.7.2.2 of the EA.***

Please see section 4.4.1.7.2.2 (page 24) of the attached EA for this information.

3. ***4.4.1.7.2 (deficiency b): The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa.***

   The information provided in the February 4, 2000 response is adequate but needs to be incorporated into section 4.4.1.7.2.4.

Please see section 4.4.1.7.2.4 (page 25) of the attached EA for this information.

4. ***4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).***

   The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.1.7.3 of the EA.

Please see section 4.4.1.7.3 (page 25) of the attached EA for this information.

5. ***4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v).***

a. ***The first 2 paragraphs deal with a summary of the effects of the drug. The discussion is acceptable but is not included in the EA text. It should be included at the end of section 4.4.1.8.***

Please see section 4.4.1.8.5 (page 35) of the attached EA for this information.

b. ***You have stated that the drug is predicted to [redacted] This statement should not be included because no formal adsorption/desorption test was performed. Based on the insolubility of the compound the potential to "settle out" in the waste water treatment process and the aquatic environment should be discussed and included in 4.4.1.7.5.***

Please see section 4.4.1.7.5 (page 26) of the attached EA for this revised discussion.

6. ***4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence.***

The information provided is adequate. However, this information needs to be included in the EA and the EA needs to be revised to delete the incorrect statements that indicate no testing was performed.

Please see sections 4.4.1.8.1.3, 4.4.1.8.2.4 and 4.4.1.8.3.2 (pages 27, 29 and 31) of the attached EA for these revisions to the daphnia, fish and algae studies, respectively.

7. ***4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7).***

You added a statement to section 4.4.4 that [redacted] This does not address the issue. An EA focuses on the potential environmental affects of the use of the drug. The mitigation measures included in the EA only pertain to the manufacturing site. Mitigation measures necessary because of any environmental affects from the use of the drug need to be discussed. The information that was added to section 4.4.4 should be deleted.

As requested, the information added to section 4.4.4 has been deleted. As stated in our February 4, 2000, no adverse environmental effects have been identified, nor are any foreseen, based on use of the drug.

8. ***4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9).***

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.5 of the EA.

This information has been included in section 4.4.5 (page 36) of the attached EA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

/S/ for

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

Attachment 1

Revised Environmental Assessment

WITHHOLD 37 PAGE (S)

Draft

GelTex PHARMACEUTICALS, INC.

May 24, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville. MD 20857

Labeling for NDA's 21-141/21-176 accepted.
/S/
5-24-00

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 019
Revised Package Insert

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As requested by Dr. David Orloff in a telephone conversation on May 23, 2000, the purpose of this submission is to provide the enclosed package inserts for Welchol™, one for the tablet dosage form (NDA 21-176) and one for the capsule dosage form (NDA 21-141).

Please note that the enclosed package inserts are intended to replace Section 2.1 (pages 3-11) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

WITHHOLD 117 PAGE (S)

Draft

Labeling

GelTex PHARMACEUTICALS, INC.

May 24, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

Labelling for NDA's 21-141/21-176 accepted.
/S/
5-24-00

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 019
Revised Package Insert

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As requested by Dr. David Orloff in a telephone conversation on May 23, 2000, the purpose of this submission is to provide the enclosed package inserts for Welchol™, one for the tablet dosage form (NDA 21-176) and one for the capsule dosage form (NDA 21-141).

Please note that the enclosed package inserts are intended to replace Section 2.1 (pages 3-11) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex
PHARMACEUTICALS, INC.

May 15, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 018
Minor Amendment: Update on Financial Disclosure Information

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As requested by Mr. William Koch in a telephone conversation on May 12, 2000, the purpose of this submission is to provide an update to the financial disclosure information contained in the original NDA.

As indicated on page 7 of Section 19 of the original NDA, at the time of filing we had been unable to obtain information attesting to the absence of financial interests and arrangements as described in 21 CFR §54.4(a)(3) from [redacted]. Since that time, we have received this information from all remaining investigators except [redacted] who has failed to return financial information [redacted]). We have continued our efforts to obtain information for the outstanding studies through repeated written requests (March 18, July 9, August 9, September 30 and December 8, 1999, January 5, 2000) and telephone contacts (January 17, February 9 and March 1, 2000) to [redacted] office.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
GelTex Pharmaceuticals, Inc.	May 15, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(781) 290-5888	(781) 434-3603
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
153 Second Avenue Waltham, MA 02451	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-141/21-176

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Colesevelam hydrochloride	Welchol™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl] trimethylammonium chloride and N-allyldecylamine, hydrochloride (IUPAC)

CODE NAME *(If any)*
GT31-104HB

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet and Capsule	625 mg (Tablet) 375 mg (Capsule)	Oral

(PROPOSED) INDICATION(S) FOR USE: Cholestagel, administered alone or in combination with HMG-CoA reductase inhibitors, is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet and exercise.

APPLICATION INFORMATION

APPLICATION TYPE (check one) CFR 314.94)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Update Financial Disclosure Information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

(See attachment)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Clinical Investigator Financial Disclosure (Form FDA 3454)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Martha J. Carter.	Martha J. Carter Vice President, Regulatory Affairs	15 May 2000.
ADDRESS *(Street, City, State, and ZIP Code)* 153 Second Avenue Waltham, MA 02451		Telephone Number (781) 434-3443

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DDHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

GelTex
PHARMACEUTICALS, INC.

May 8, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 017
Minor Amendment: Chemistry, Manufacturing and Controls

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As discussed with Mr. William Koch in a telephone conversation on May 8, 2000, the purpose of this submission is to provide a correction to the drug substance specification for "Total titratable amines."

The specification for total titratable amines is set in the NDA at —— mmoles amine/gram. The target for the commercial campaign is — mmoles amine/gram, and is based on the mean titratable amine level in the final pilot plant campaign ("Procedure 2" – see attached Table 4.1-23f from Appendix 4.1-23 of the NDA). If the range is centered around this value, the specification should be —— mmoles amine/gram. All of the batches produced that were used in clinical trials fall within this range.

Enclosed is Table 4.1-37 from the original NDA, with the corrected specification indicated with highlighted text. This information is intended to replace pages 76-77 in Section 4.1 of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter
Vice President, Regulatory Affairs

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
GelTex Pharmaceuticals, Inc.	May 8, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(781) 290-5888	(781) 434-3603
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
153 Second Avenue Waltham, MA 02451	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-141/21-176

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Colesevelam hydrochloride	Welchol™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl] trimethylammonium chloride and N-allyldecylamine, hydrochloride (IUPAC)

CODE NAME *(If any)*
GT31-104HB

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet and Capsule	625 mg (Tablet) 375 mg (Capsule)	Oral

(PROPOSED) INDICATION(S) FOR USE: Cholestagel, administered alone or in combination with HMG-CoA reductase inhibitors, is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet and exercise.

APPLICATION INFORMATION

APPLICATION TYPE (check one) CFR 314.94)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Correction in Drug Substance Specification

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(See attachment)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

(See attachment)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify) Clinical Investigator Financial Disclosure (Form FDA 3454)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
For Martha J. Carter	Martha J. Carter Vice President, Regulatory Affairs	May 8, 2000
ADDRESS *(Street, City, State, and ZIP Code)* 153 Second Avenue Waltham, MA 02451		Telephone Number (781) 434-3443

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DDHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

WITHHOLD 4 PAGE (S)

GelTex
PHARMACEUTICALS, INC.

April 28, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 016
Revised Package Insert

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As requested by Mr. William Koch in a telephone conversation on April 27, 2000, the purpose of this submission is to provide two package inserts for Welchol™, one for the tablet dosage form (NDA 21-176) and one for the capsule dosage form (NDA 21-141). The text in the attached package inserts is identical to that submitted on April 26, 2000, except for this modification. The enclosed package inserts are intended to replace Section 2.1 (pages 3-11) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

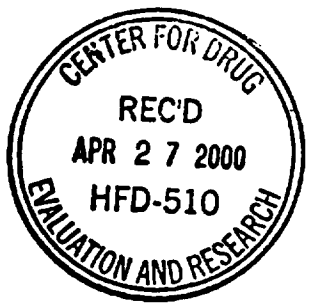
GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

DV

April 26, 2000



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 015
Revised Package Insert
Revised Bottle and Carton Labels

Dear Sir/Madam:

Reference is made to the above captioned NDAs for Welchol™ (colesevelam hydrochloride), submitted on July 30, 1999. As discussed with Mr. William Koch and Drs. Ronald Steigerwalt and Gemma Kuijpers in a telephone conversation on April 25, 2000, the purpose of this submission is to provide new draft labeling for Welchol™. The enclosed version of the package insert incorporates changes agreed to during a teleconference with the Division on April 19, 2000, as well as the inclusion of capsule information as requested by Mr. William Koch on April 25, 2000. The enclosed package insert is intended to replace Section 2.1 (pages 3-11) of the original NDA.

Also enclosed are revised bottle and carton labels to reflect the Welchol™ trade name and other minor changes, as well as to include capsule labels. The enclosed bottle and carton labeling is intended to replace Sections 2.2-2.5 (pages 2-5) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACT
☐ MEMO
CSO LS DATE

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

bc

April 25, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 014
Response to April 25, 2000 Request
Environmental Assessment

Dear Sir/Madam:

Reference is made to the NDAs cited above for Welchol™ (colesevelam hydrochloride), and to their submission date of July 30, 1999. Further reference is made to a telephone conversation with Nancy Sager on April 25, 2000, during which Ms. Sager requested a clean copy of the environmental assessment (EA).

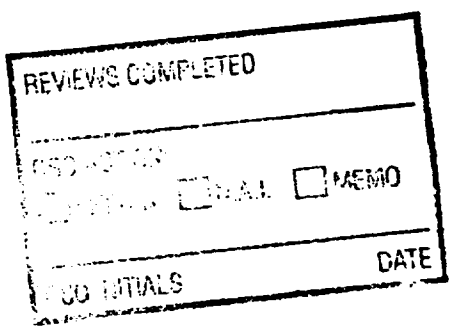
The purpose of this submission is to provide the requested environmental assessment. Please note that the EA is identical to that submitted on March 23, 2000, except that the trade name has been changed to "Welchol™" throughout.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs



153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

MC

April 20, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141, 21-176
Welchol™ (colesevelam hydrochloride)
Amendment 013
Chemistry, Manufacturing and Controls
Stability Update
Change from — Count to 24-Count Sample Bottle

Dear Sir/Madam:

Reference is made to the NDAs cited above for Welchol™, submitted July 30, 1999. As discussed with Dr. Martin Haber in telephone conversations of February 10, and April 12, 2000, the purpose of this submission is to provide an amendment describing a change in the physician sample packaging from a — to a 24-count bottle, as well as to provide a stability update for these NDAs.

Please note that a revised bottle label to reflect this change in tablet count, as well as to replace the Cholestagel trade name with Welchol™ on all labels, will be submitted with the revised package insert in a separate amendment.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

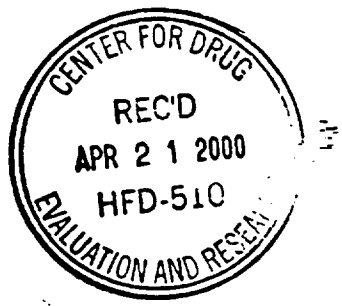
153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

DC



April 20, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 013
Chemistry, Manufacturing and Controls
Stability Update
Change from — Count to 24-Count Sample Bottle

Dear Sir/Madam:

Reference is made to the NDAs cited above for Welchol™, submitted July 30, 1999. As discussed with Dr. Martin Haber in telephone conversations of February 10, and April 12, 2000, the purpose of this submission is to provide an amendment describing a change in the physician sample packaging from a — to a 24-count bottle, as well as to provide a stability update for these NDAs.

Please note that a revised bottle label to reflect this change in tablet count, as well as to replace the Cholestagel trade name with Welchol™ on all labels, will be submitted with the revised package insert in a separate amendment.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

NDA BC

April 18, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Welchol™ (colesevelam hydrochloride)
Amendment 012
Response to Request for Information

Dear Sir/Madam:

Reference is made to the NDAs cited above for Welchol™, submitted July 30, 1999. As requested by Dr. Robert Shore in a telephone conversation of April 14, 2000, the purpose of this submission is to provide the following justification to support the bile acid binding and disintegration specifications for Welchol™.

Bile Acid Binding
The specification for bile acid binding for Welchol™ tablets is:

glycocholic acid:	—— g GC/g drug substance in the drug product
glycochenodeoxycholic acid:	—— g GCDC/g drug substance

This is the same specification as proposed for the bulk drug substance. There have been — lots of drug substance produced during the IND phase of the program at pilot scale. The results for bile acid binding are:

Bile acid	Average	Min.	Max.
GC	0.59 g/g	— g/g	— g/g
GCDC	1.59 g/g	— g/g	— g/g

The results reported for the tablet lot analyses in Table 4.2.29 are generated by preparing a composite sample from five tablets, performing the bile acid binding tests in duplicate for each bile acid, and calculating the amount of bile acid bound per gram of drug substance present in the sample. The result reported in the table is the mean of the two replicates.

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

The bile acid binding specification for Welchol™ can be justified because it is the same specification as used for the drug substance. The specification range can be justified due to the observed range for the lots of drug substance that have been manufactured to date. We feel the specification and range are appropriate for both the drug substance and drug product for control of bile acid binding of this product. All lots of drug substance and drug product manufactured to date have met the specification for bile acid binding.

Disintegration

The proposed specification for disintegration of the tablet drug product is complete disintegration in not less than — minutes. The specification for the capsule drug product is the same. This drug is insoluble so a dissolution specification is not appropriate.

The specification time limit was established to ensure that the drug product was disintegrated as the product exited the stomach.

Disintegration is determined according to cUSP <701>. Six units are placed in a temperature controlled disintegration apparatus with the specified disintegration medium. The time required for the last unit to fully disintegrate is the measured disintegration time. The capsules and tablets are tested by identical methods.

Disintegration for all lots of capsule drug product used for the clinical studies ranged from —minutes to — minutes (please see Table 4.2-8 of the NDA). The lots used for the two Phase 3 clinical studies were —and — minutes, respectively.

The specification for the tablet drug product was selected to be the same as the capsule drug product (please see Table 4.2-29 of the NDA). This specification adequately controls the disintegration of both the tablet and capsule drug product and can be justified based on the clinical experience with the capsules. At some time in the future the specification limit of a disintegration time of less than — minutes could be re-evaluated after an adequate number of commercial lots have been manufactured. All lots of tablet and capsule drug product manufactured to date conform to the current specification.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter
Vice President, Regulatory Affairs

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

bL

CENTER FOR DRUG
REC'D
APR 10 2000
HFD-510
EVALUATION AND RESEARCH

BEST POSSIBLE COPY

April 7, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA [redacted]/21-176
Colesevelam hydrochloride
Amendment 011
Proposed Changes to Package Insert

Dear Sir/Madam:

Reference is made to the above captioned NDAs for colesevelam hydrochloride, submitted on July 30, 1999. As discussed with Bill Koch in a telephone conversation with Dean Alger on April 7, 2000, the purpose of this submission is to provide new draft labeling for colesevelam hydrochloride. Revisions to the package insert were made at the request of Sankyo Parke Davis, who will be marketing colesevelam hydrochloride for GelTex Pharmaceuticals. The enclosed package insert is intended to replace Section 2.1 (pages 3-11) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED
[redacted]
☐ LETTER ☐ N.A.I. ☐ MEMO
COPIES DATE

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex
PHARMACEUTICALS, INC.

[redacted]

bv

April 7, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/[redacted]
Colesevelam hydrochloride
Amendment 011
Proposed Changes to Package Insert

Dear Sir/Madam:

Reference is made to the above captioned NDAs for colesevelam hydrochloride, submitted on July 30, 1999. As discussed with Bill Koch in a telephone conversation with Dean Alger on April 7, 2000, the purpose of this submission is to provide new draft labeling for colesevelam hydrochloride. Revisions to the package insert were made at the request of Sankyo Parke Davis, who will be marketing colesevelam hydrochloride for GelTex Pharmaceuticals. The enclosed package insert is intended to replace Section 2.1 (pages 3-11) of the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

OSO ACTION:
☐ LETTER ☐ E-MAIL ☐ VERBAL

OSE INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

March 30, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Colesevelam hydrochloride
Amendment 010
Historical Control Data from [redacted]

Dear Sir/Madam:

Reference is made to the NDAs cited above for colesevelam hydrochloride, submitted July 30, 1999. As requested by Dr. Gemma Kuijpers in a telephone conversation with Martha Carter on March 16, 2000, the purpose of this submission is to provide historical control data for selected lesions identified from the colesevelam hydrochloride rat and mouse carcinogenicity studies. Please note that the Sprague-Dawley rat strain reported here is different from the strain used in the colesevelam hydrochloride carcinogenicity study.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

82

BEST POSSIBLE COPY

March 30, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/[redacted]
Colesevelam hydrochloride
Amendment 009
Response to March 27, 2000 Facsimile

Dear Sir/Madam:

Reference is made to the NDA cited above for colesevelam hydrochloride, and to the Agency's facsimile of March 27, 2000 containing comments from the Clinical Pharmacology and Biopharmaceutics reviewer.

The purpose of this submission is to respond to your comments. For ease of review, the Agency's requests/comments are repeated in ***bold italics***, followed by our responses.

1. ***As per the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs," page 16, the sponsor should provide proposed draft labeling in a word processing format (The FDA standard is currently Word).***

As confirmed with Dr. Robert Shore on March 28, 2000, this request has been satisfied previously. A diskette containing Word files of the draft labeling from the NDA was submitted as a desk copy to Margaret Simoneau on October 5, 1999.

2. ***The release specs for Cholestagel include bile acid binding and disintegration. The actual data used to set the proposed specs could not be located in the submission. If they are included, the sponsor should indicate where they are; if not included, the sponsor should submit these data for evaluation.***

Please see Tables 4.2-8 (page 28) and 4.2-29 (page 70) of the NDA for lot analysis data for capsules and tablets, respectively.

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

3. ***A ^{14}C-labeled colesevelam ADME study in humans is referred to as study GTC-48-803 and GTC-37-803. The sponsor should clarify if this is the same study or if two studies were done.***

Study GTC-48-803 is the correct study number. This study was inadvertently referred to as GTC-37-803 in Section 8.15.2.1 (page 73).

4. ***It is indicated that the lots used in the in vitro bioequivalence study are: caps - EC75M, EC76M, EC78M; and tablets – EJ54M, EK12MB, UPM9901. The production size and formulation of most of these lots could not be located in the submission. If this information is included, the sponsor should indicate where it is; if not included, the sponsor should submit this information.***

Although some of this information can be found throughout Section 4 of the NDA, for ease of review, the production size and formulation of the requested lots are provided in the following four tables.

Capsule Production Size

LOT NUMBER	PRODUCTION SIZE
EC75M	[redacted] Capsules
EC76M	[redacted] Capsules
EC78M	[redacted] Capsules

Capsule Formulation

LOT NUMBER	FORMULATION	
	Component	mg/tablet
EC75M, EC76M, and EC78M	Colesevelam Hydrochloride	375 mg
	Magnesium Stearate	[redacted]

APPEARS THIS WAY
ON ORIGINAL

Tablet Production Size

LOT NUMBER	PRODUCTION SIZE
EJ54M	[redacted] Tablets
EK12MB	[redacted] Tablets
UPM9901	[redacted] Tablets

Tablet Formulation

LOT NUMBER	FORMULATION	
	Component	**mg/tablet**
EJ54M, EK12MB, and UPM9901	Colesevelam Hydrochloride	625.0
	———	———
	Microcrystalline Cellulose	———
	Magnesium Stearate, NF	———
	Silicon Dioxide, NF	———
	———	———
	———	———

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

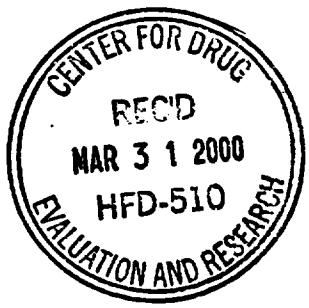
NEW CORRESP.

NC

GelTex PHARMACEUTICALS, INC.

March 30, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-141[redacted]
Colesevelam hydrochloride
Amendment 008
Patent Information
Debarment Certification

BEST POSSIBLE COPY

Dear Sir/Madam:

Reference is made to the NDA cited above for colesevelam hydrochloride, submitted July 30, 1999. As requested by Ms. Margaret Simoneau in a telephone conversation with Dean Alger on March 28, 2000, the purpose of this submission is to submit Section 13 "Patent Information" and Section 16 "Debarment Certification" to the NDAs cited above. Please note that with the exception of the revised dates and the elimination of the name Cholestagel®, this information is identical to that submitted in the original NDA.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ E.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

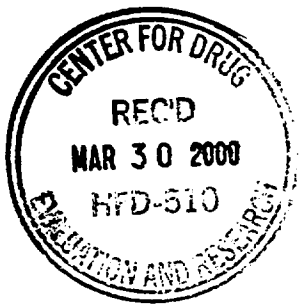
153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

[redacted]

SV



March 29, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141[redacted]
Colesevelam hydrochloride
Amendment 007
Safety Update Report

Dear Sir/Madam:

Reference is made to the NDAs cited above for colesevelam hydrochloride, submitted July 30, 1999. As requested by Ms. Margaret Simoneau in a telephone conversation with Dean Alger on March 28, 2000, the purpose of this submission is to provide a Safety Update Report.

Please note that there is no new safety information to report for colesevelam hydrochloride at this time. There have been no ongoing or new clinical studies conducted with the drug since the submission was prepared. The Integrated Summary of Safety and the Risk-Benefit Discussion remain unchanged from the original submission.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

ORIGINAL

NEW CORRESP

GelTex PHARMACEUTICALS, INC.

March 27, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 21-176
Colesevelam hydrochloride
Amendment 006
Replacement of Cholestagel® trade name with Welchol™

Dear Sir/Madam:

Reference is made to the NDA cited above for colesevelam hydrochloride and to a March 27, 2000 telephone conversation between Dean Alger of GelTex and Margaret Simoneau of CDER. As discussed with Ms. Simoneau, the purpose of this submission is to provide data that support the choice of the name Welchol™ to replace Cholestagel®. Included in this submission is a report by _____ describing the research conducted with physicians and pharmacists, which led to the recommendation of the name Welchol™. Ten copies of the report are being provided for ease of review.

We will be happy to discuss this research with you, either in person or by teleconference, at your earliest convenience.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex
PHARMACEUTICALS, INC.

ORIGINAL

BC

March 8, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141/21-176
Colesevelam hydrochloride
Amendment 004
Response to February 14, 2000 Facsimile Regarding CMC Section Comments

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Dear Sir/Madam:

Reference is made to the NDAs cited above for colesevelam hydrochloride, and to the Agency's facsimile of February 14, 2000 containing comments on Section 4.

The purpose of this submission is to respond to your comments, and to provide the requested information in Attachments 1-8. For ease of review, the Agency's requests/comments are repeated in ***bold italics***, followed by our responses.

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

WITHHOLD 3 PAGE (S)

With regard to the Labeling: The description section is too long and detailed. Please delete the second paragraph and try to simplify the other text.

Following is a revised *Description* section of the draft package insert (Section 2.1.1 of the NDA) with the second paragraph deleted and a simplified version of the remaining text. We will resubmit revised labeling in its entirety as appropriate during the review process.

Description

Welchol™ contains colesevelam hydrochloride, a non-absorbed, polymeric, lipid-lowering agent intended for oral administration. Colesevelam ——— has ——— Colesevelam ——— is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. ——— Colesevelam ——— is hydrophilic, — and insoluble in water.

Welchol™ is an off-white, solid tablet containing 625 mg colesevelam ——— In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, and silicon dioxide. ——— The tablets are imprinted using a water-soluble black ink.

Also, please note that a routine review of Section 4 the NDA has revealed two minor errata, which are itemized and corrected in **Attachment 8**.