

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-141 and 21-176**

**CHEMISTRY REVIEW(S)**

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 21- 141/21-176

DATE REVIEWED: May 23, 2000

CHEMISTRY REVIEW #: 3

REVIEWER: Martin Haber, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>
AMENDMENT	5/8/00	5/9/00

NAME & ADDRESS OF SPONSOR: GelTex Pharmaceuticals  
153 Second Ave  
Waltham, MA 02451 (781) 434-3443

DRUG PRODUCT NAME:  
Proprietary: Welchol (previously Cholestagel)  
Nonproprietary: Colesevelam Hydrochloride  
Code Name/#: GT31-104HB  
Chem.Type/Therapeutic.Class: Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of hypercholesterolemia

DOSAGE FORM: Capsules and Tablets

STRENGTHS: 375 mg Capsule, 625 mg Tablet

ROUTE OF ADMINISTRATION: Oral

Rx/OTC:  X Rx  OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-, chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride. For structural formula, see review #1. Colesevelam hydrochloride is a cross-linked polymer.

REMARKS:

This review covers amendments to NDA 21-141 and NDA 21-176 for capsules and tablets, respectively. Both formulations use the same drug substance, colesevelam HCl, a non-absorbed bile acid sequestration agent. User fee date is 5/30/00. The 5/8/00 amendment provides for a correction to the drug substance specification for total titratable amines. Final EA consult review on the firm's response to EA deficiencies was satisfactory. EES status is satisfactory.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint the application is approvable.

Orig. NDA # 21- 141, NDA # 21-176

cc: HFD-510/Division files/J.Gibbs/S.Koepke/D-G.Wu/M.Haber/W.Koch

R/D Init by: Dr. D-G. Wu, Team Leader Chemist

/S/

5/24/00

/S/  
Martin Haber, Ph.D.  
Review Chemist

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510  
Review of Chemistry, Manufacturing, and Controls

NDA #: 21- 141/21-176

DATE REVIEWED: April 17, 2000

CHEMISTRY REVIEW #: 2

REVIEWER: Martin Haber, Ph.D.

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

AMENDMENT

3/8/00

3/9/00

AMENDMENT

4/20/00

4/21/00

NAME & ADDRESS OF SPONSOR:

GelTex Pharmaceuticals  
153 Second Ave  
Waltham, MA 02451 (781) 434-3443

DRUG PRODUCT NAME:

Proprietary:

Welchol (previously Cholestagel)

Nonproprietary:

Colesevelam Hydrochloride

Code Name/#:

GT31-104HB

Chem. Type/Therapeutic Class:

Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION:

Treatment of hypercholesterolemia

DOSAGE FORM:

Capsules and Tablets

STRENGTHS:

375 mg Capsule, 625 mg Tablet

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

X Rx    OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-, chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride. For structural formula, see review #1. Colesevelam hydrochloride is a cross-linked polymer.

REMARKS:

This review covers amendments to NDA 21-141 and NDA 21-176 for capsules and tablets, respectively. Both formulations use the same drug substance, colesevelam HCl, a non-absorbed bile acid sequestration agent. User fee date is 5/30/00. The 3/8/00 amendment provides for responses to CMC deficiencies forwarded to the applicant on 2/14/00. The core CMC deficiencies have been satisfactorily addressed and remaining issues are EA consult review, tradename, cGMP inspection and labeling. The 4/20/00 amendment provides for a change in the physician sample packaging from a — to a 24-count bottle (tablets) and a stability update. Final EA consult review on the firm's response to EA deficiencies is pending. After OPDRA tradename review found the name "Cholestagel" unacceptable, and the new name, "Welchol", also unacceptable, the new name was found acceptable by the clinical director. EES status is pending. For specific chemistry comments, see Review notes.

CONCLUSIONS & RECOMMENDATIONS:

A satisfactory response to chemistry deficiencies has been made. From a chemistry viewpoint the application is approvable, pending a satisfactory EA consult review and acceptable cGMP status.

Orig. NDA # 21- 141, NDA # 21-176

cc: HFD-510/Division files/J.Gibbs/S.Koepke/D-G.Wu/M.Haber/W.Koch

R:D Init by: Dr. D-G. Wu, Team Leader Chemist

IS/  
Martin Haber, Ph.D.  
Review Chemist

IS/

4/25/00

