CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20375/S007

CORRESPONDENCE

NDA 20-375/S-007

APR 18 1997

Berlex laboratories, Inc.
Attention: Ms. Sharon W. Brown
Associate Director,
Drug Regulatory Affairs
300 Fairfield Road
Wayne, NJ 07470-7358

Dear Ms. Brown:

We acknowledge your supplemental new drug application dated October 18, 1996, received October 29, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Climara® (estradiol transdermal system).

The User Fee goal date for this application is April 18, 1997.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) because of deficiencies in your referenced DMF, These deficiencies were previously communicated to you on February 10, 1997. Until the deficiencies noted in DMF are corrected, the application cannot be approved.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

/S/ 4/17/97

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of New Drug Chemistry II
@ Division of Reproductive and Urologic Drug Products HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20375
HFD-580/Div. files
HFD-820/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-580/D.Moore
HFD-580/AMitra/MRhee/LRarick

Drafted by: dm/April 14, 1997/n20375. S07

/S/ 4/17/97

Concurrences:
LPauls, AMitra, MRhee 04.17.97

NOT APPROVABLE (NA)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-375/S-007

OCT 29 1996

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358

Attention: Jo-Ann M. Ruane
Manager
Drug Regulatory Affairs

Dear Ms. Ruane:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Climara (estradiol transdermal system)

NDA Number: 20-375

Supplement Number: S-007

Date of Supplement: October 18, 1996

Date of Receipt: October 21, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 20, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Lana Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-375/S-007
HFD-580/Div. Files
HFD-580/CSO/Moore

SUPPLEMENT ACKNOWLEDGEMENT

BERLEX

AC007 - Dm 9/24/97

TELEFAX
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

August 13, 1997

NEW CORRESP

Noted Krahyer 9/16/97

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

9/4/97

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 20 1997
HFD-580

RE: NDA 20-375, Supplement 007
Climara® (estradiol transdermal system)

Dear Dr. Rarick

Please refer to our approved New Drug Application 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994. This NDA was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995.

Further reference is made to Supplement 007 which was dated October 18, 1996. This supplement provides for the use of estradiol substance, EP grade. Reference is also made to the not approvable letter dated April 18, 1997 and the options provided pursuant to 21 CFR 314.120. The not approvable letter relates to deficiencies in DMF The letter requested that Berlex notify the Division within 10 days after receipt of the April 18 letter. Berlex notified the Division on May 9, 1997 that we intend to submit an amendment.

Finally, reference is made to a telephone conversation on August 13 between your representative, Ms. Diane Moore, and the undersigned. During this conversation, Ms. Moore informed Berlex that in order to complete the review of Supplement 007, Berlex will need to submit a letter which allows for the review of the DMF.

This letter amends Supplement 007 by providing two letters. The letter dated June 4, 1997 authorizes the FDA to refer to information in the DMF. Also attached, for information, is a copy of the letter dated June 24, 1997 from which responds to the deficiencies in DMF

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS
9/11/97
DATE

Please contact the undersigned if you have any questions or need additional information at (973) 276-2162

Sincerely,

BERLEX LABORATORIES

Sharon W. Brown
Associate Director
Drug Regulatory Affairs

SB/letter/clima105

TELEFAX
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

BERLEX

Berlex Laboratories
Division of Berlex Laboratories, Inc.

300 Fairfield Road
Wayne, NJ 07470-7358
Telephone: (201) 694-4100
Fax: (201) 694-9093

ORIGINAL

SUPPL NEW CORRESP

May 9, 1997

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

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

RE: NDA 20-375, Supplement 007
Climara® (estradiol transdermal system)

Dear Dr. Rarick:

Please refer to our approved New Drug Application 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994. This NDA was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995.

Further reference is made to Supplement 007 which was dated October 18, 1996. This supplement provides for the use of estradiol substance, EP grade. Reference is also made to the not approvable letter dated April 18, 1997 and the options provided pursuant to 21 CFR 314.120. The letter requested that Berlex notifiy the Division within 10 after receipt of the April 18 letter.

Finally, reference is made to a April 30, 1997 voicemail message to your representative, Ms. Diane Moore and the undersigned. In the voicemail, Berlex stated our intentions to submit an amendment to S-007. This letter confirms our intention to submit an amendment.

Please contact the undersigned if you have any questions or need additional information at (201) 305-5329 until May 19, 1997. After May 19, please contact me at (201) 276-2162

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 13 1997
HFD-580

Sincerely,

BERLEX LABORATORIES

Sharon W. Brown
Associate Director
Drug Regulatory Affairs

SB/letter/clima070

Orig

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

300 Fairfield Road
Wayne, NJ 07470-7858
Telephone: (201) 694-4100
Fax: (201) 694-9092

UPS OVERNIGHT

NDA NO. 20-375 REF. NO. 5-002
NDA SUPPL FOR Contents

REVIEW ☐ MEMO
CSO ACTION: ☐ LETTERS ☐ N.A.L. DATE
CSO INITIALS

REC'D
OCT 21 1996
HFD-580

October 18, 1996

Dr. Lisa Rarick, Director
Division of Reproductive and Urological Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, WOC II, Room 6027
Rockville, MD 20857-1706

Re: NDA 20-375
Climara® (estradiol transdermal system)
Supplement: Alternate Manufacturing Process for the Drug Substance

Dear Dr. Rarick,

Reference is made to our New Drug Application 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994. This NDA was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995.

Reference is also made to S-002, submitted on January 26, 1995 and approved on February 28, 1995, which provides for Berlex's parent company, as a manufacturer of the drug substance, Estradiol USP.

Pursuant to 21 CFR 314.70(b)(1)(iv), this supplemental application is being submitted to provide for an alternate manufacturing process for the drug substance, estradiol USP, manufactured by The drug substance produced by the alternate manufacturing process is manufactured at the same facility as the approved drug substance and the synthetic route for both processes is the same. The primary difference between the alternate and approved processes is the inclusion of two additional purification steps in the manufacture of the alternate material. While both the approved and alternate manufacturing processes result in drug substance which meets the requirements of the USP, estradiol produced by the alternate process also meets the tighter specifications set forth in the corresponding monograph of the European Pharmacopoeia (EP) with respect to related substances. Approval of the EP/USP-grade drug substance will allow for the production of drug product which is suitable for both the U.S. and European markets.

Provided in this supplement is chemistry, manufacturing and controls information for the drug substance produced by the alternate manufacturing process as well as stability data for drug product produced with the alternate material. Drug Master File No. for estradiol was updated on June 7, 1996, and includes detailed manufacturing, control, analytical and stability information pertaining to the drug substance produced by the alternate process. A letter authorizing the FDA to refer to this DMF on behalf of Berlex Laboratories is provided in this supplement.

In addition to the Archival and Review Copies submitted herein, a Field Copy of this supplement is being provided to the FDA District Office in Parsippany, NJ. Each Copy of this application contains the appropriate Field Copy certification statement and debarment certification statement.

Please contact the undersigned at (201) 305-5123 if you have any questions pertaining to this supplement.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane
Manager
Drug Regulatory Affairs

JMR/188

Enclosures