

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-375/S-009**

**ADMINISTRATIVE DOCUMENTS**

# MINUTES of TELECON

**Date:** March 12, 1998      **Time:** 9:33 - 9:35 AM      **Location:** Parklawn; Mrs. Moore's Office

**NDA:** 20-375/S-009      **Drug Name:** Climara (estradiol transdermal system) 0.1 mg/day and 0.05 mg/day

**External Participant:** Berlex Laboratories

**Type of Meeting:** Chemistry Advice

**Meeting Chair:** Dr. Amit Mitra

**External Participant Lead:** Mr. Jeffrey Millington

**Meeting Recorder:** Mrs. Diane Moore

## FDA Attendees:

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

## External Constituents:

Jeffrey Millington - Manager, Drug Regulatory Affairs

## Meeting Objectives:

To convey an error in the **DESCRIPTION** section of the labeling submitted in Supplement 009 to NDA 20-375.

## Discussion Points:

- on the first page of the physician's labeling, under the **DESCRIPTION** section, the sponsor lists two dosages of the drug; the label should include a third dosage

## Decisions reached:

- the sponsor should submit a letter to the NDA to correct the error

## Action Items:

- | Item:                            | Responsible Person: | Due Date: |
|----------------------------------|---------------------|-----------|
| • submit letter to correct error | Mr. Millington      | Two days  |

                    / S /                          3/23/98  
Signature, minutes preparer

                    / S /                          3/23/98  
Concurrence, Chair

drafted: dm/March 12, 1998/n20375S009031298

NDA 20-375/S-009

Page 2

Minutes of Telecon - March 12, 1998

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/MMann/MRhee/AMitra/JMercier

Concurrence:

LPauls 03.17.98/AMitra 03.20.98



---

**TELEFAX  
CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

**Drug Development & Technology**  
Division of Berlex Laboratories, Inc.

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

---

March 12, 1998

Lisa Rarick, M.D., Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation II, HFD-580  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5800 Fishers Lane  
Room 17B-45  
Rockville, Maryland 20857-1706

Re: **NDA 20-375**  
**Climara® (estradiol transdermal system)**  
**Amendment to Supplement 009: Intermediate Strength**  
**Patch**  
**Response to FDA Request for Information**

---

Dear Dr. Rarick:

Reference is made to our NDA 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994 and was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995. The NDA provides for two patch sizes, 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup>.

We refer to the supplement submitted on September 19, 1997 which supports an 18.75 cm<sup>2</sup> intermediate patch size. This intermediate size patch is identical in all respects to the approved 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup> patch sizes. The only difference is in the surface area of the patch which is cut with a different size die. The roll stock for the 3 patch sizes is the same.

Climara\* (estradiol transdermal system)

March 12, 1998

Page 2

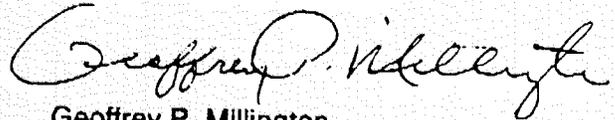
Reference is also made to telephone communication between your representative, Ms. Diane Moore, Reviewing Chemist, Dr. Mitra, and the undersigned on March 12, 1998 wherein Ms. Moore and Dr. Mitra requested that Berlex submit a correction of the draft labeling (S-009, page 4 00001) which would provide the estradiol content of the 18.75 cm<sup>2</sup> patch.

Attached are two copies of the corrected page of the draft labeling. The correction, under the heading "Description", is an addition of "5.85" which represents the estradiol content in mg for the intermediate strength patch.

Please contact the undersigned at (973) 276-2254 if you have any questions concerning this supplement.

Sincerely,

BERLEX LABORATORIES



Geoffrey P. Millington

Manager

Drug Regulatory Affairs

Desk Copy: Ms. Diane Moore

GPMletter/clima025



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-375/S-009

Food and Drug Administration  
Rockville MD 20857

OCT - 8 1997

Berlex Laboratories, Inc.  
340 Changebridge Rd.  
Montville, NJ 07045

Attention: Geoffrey Millington  
Manager, Drug Regulatory Affairs

Dear Mr. Millington:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Climara (estradiol transdermal system)

NDA Number: 20-375

Supplement Number: S-009

Date of Supplement: September 19, 1997

Date of Receipt: September 24, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 23, 1997 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,

*ISI* *MA*  
Lana L. Pauls, M.P.H.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 20-375/S-009  
Page 2

cc:

Original NDA 20-375/S-009  
HFD-580/Div. Files  
HFD-580/CSO/

**SUPPLEMENT ACKNOWLEDGEMENT**

# BERLEX

## ORIGINAL

**Drug Development & Technology**  
Division of Berlex Laboratories, Inc.

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

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

NDA NO. 20-375 REF. NO. 009  
NDA SUPPL FOR 565

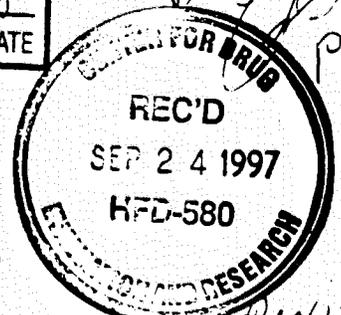
September 19, 1997

REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS      DATE
<i>AP</i> <i>3/23/98</i>

*Noted  
Have people  
check for  
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10/19/97*

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

*Noted  
Kralog  
10/17/97*



*Revised  
Code for  
Drug Ant. DA  
3-17-98      10-17-97*

Re: NDA 20-375  
Climara® (estradiol transdermal system)  
Supplement: Addition of Intermediate Patch Size 18.75 cm<sup>2</sup>

Dear Dr. Rarick,

Reference is made to our NDA 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994 and was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995. The NDA provides for two patch sizes, 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup>.

*Received  
Dorantey  
2/23/98*

Pursuant to 21 CFR 314.70(b)(2), this one volume supplemental application provides for the addition of an intermediate patch size of 18.75 cm<sup>2</sup>. The documentation to support this change is provided in the amendment submitted by 3M Pharmaceuticals to their DMF on September 18, 1997. Enclosed is a copy of the DMF amendment cover letter which authorizes the Division to review this amendment in association with this supplemental application.

Dr. Lisa Rarick  
September 19, 1997  
Page 2

Four copies of draft labeling (including labels for patch, pouch and carton) are provided.

Archival and Review Copies are submitted herein and each copy of this application contains the appropriate debarment certification statement.

Please contact the undersigned at (973) 276-2254 if you have any questions concerning this supplement.

Sincerely,

BERLEX LABORATORIES



Geoffrey P. Millington  
Manager  
Drug Regulatory Affairs

GPM/letter/clima016

Enclosures

CERTIFIED MAIL  
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SUPL NEW CORRESP

ORIGINAL

**BERLEX**

April 27, 1998

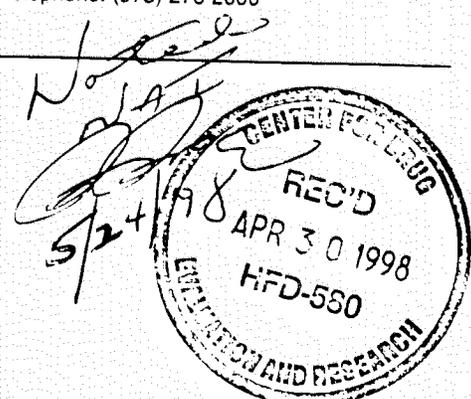
REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS <i>[Signature]</i> DATE <i>5/16/98</i>

**Drug Development & Technology**  
Division of Berlex Laboratories, Inc.

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

Lisa Rarick, M.D., Director  
Division of Reproductive & Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA SUPP AMEND**  
*S05-009*  
*ERIC*



Re: NDA 20-375

Climara® (estradiol transdermal system)  
Supplement S-009: Intermediate Strength Patch, 18.75 cm<sup>2</sup>  
General Correspondence: Submission of Patent Information

*Noted for [Signature] 5/14/98*

Dear Dr. Rarick:

Reference is made to NDA 20-375 for Climara® (estradiol transdermal system), approved by FDA on December 22, 1994. Further reference is made to Supplement S-009, which Berlex Laboratories, Inc. submitted to the Division on September 19, 1997, to support the addition of an intermediate strength patch, a 18.75 cm<sup>2</sup> system to provide delivery of 0.075 mg estradiol per day. Supplement S-009 was approved by the Division on March 23, 1998.

*Noted for [Signature] 5/15/98*

Provided herewith are two copies of our April 23, 1998 submission to the Data Base Management and Services Branch, HFD-93, which provided the Branch with "Time Sensitive Patent Information" pertaining to the 18.75 cm<sup>2</sup> intermediate strength system, in accord with the regulations cited under 21 CFR 314.53.

I can be contacted on (973) 276-2157 with regard to any questions concerning the information contained in this submission.

Sincerely,  
BERLEX LABORATORIES, INC.

*[Signature: Geri A. Besta]*  
Geri A. Besta  
Manager, Regulatory Submissions  
and Information  
Drug Regulatory Affairs

Enclosure

CERTIFIED MAIL  
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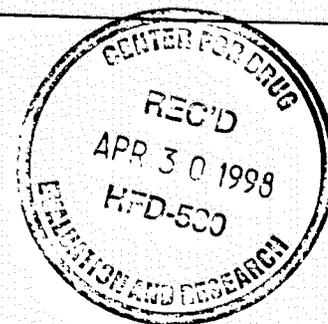
**BERLEX**

April 23, 1998

**Drug Development & Technology**  
Division of Berlex Laboratories, Inc.

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

Mary Ann Holovac, R.Ph.  
Data Base Management and Services Branch, HFD-93/NLRC  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



**Re: NDA 20-375: Climara® (estradiol transdermal system)  
Supplement S-009: Intermediate Strength Patch, 18.75 cm<sup>2</sup>  
TIME SENSITIVE PATENT INFORMATION**

Dear Ms. Holovac:

Reference is made to NDA 20-375 for Climara® (estradiol transdermal system), approved by FDA on December 22, 1994, for two systems: a 12.5 cm<sup>2</sup> system to provide delivery of 0.05 mg estradiol per day; and a 25.0 cm<sup>2</sup> system to provide delivery of 0.1 mg estradiol per day, for the treatment of moderate to severe vasomotor symptoms associated with menopause. NDA 20-375 was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995.

Reference is also made to Supplement S-009, which Berlex Laboratories, Inc. submitted to the Division of Reproductive and Urologic Drug Products, HFD-580 on September 19, 1997, to support the addition of an intermediate strength patch, a 18.75 cm<sup>2</sup> system to provide delivery of 0.075 mg estradiol per day. Supplement S-009 was approved by FDA on March 23, 1998. A copy of the Division's letter notifying Berlex of the approval of this supplement is enclosed.

Pursuant to 21 CFR 314.53(d)(2)(i)(C); 314.53(d)(2)(ii); and 314.53(d)(4), provided herewith is patent information and a patent certification, as required under 21 CFR 314.53(c)(1) and (2). Two copies of this patent information are being provided to the Branch; one copy is contained in an Archival Copy, and the other copy is contained in a Chemistry Manufacturing and Controls Section Review Copy.

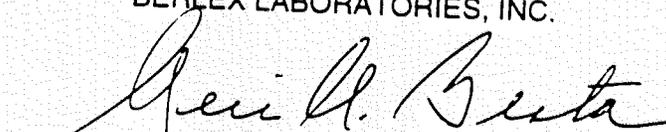
NDA 20-375: Climara® (estradiol transdermal system)  
Supplement S-009: Intermediate Strength Patch, 18.75 cm<sup>2</sup>  
TIME SENSITIVE PATENT INFORMATION  
April 23, 1998  
Page 2 of 2

It is anticipated that, in accord with CFR 314.53(e), information pertinent to the intermediate strength Climara® (estradiol transdermal system) will be reflected in the April 1998 Supplement to the Approved Drug Products with Therapeutic Equivalence Evaluations ["Orange Book"].

I can be contacted on (973) 276-2157 with regard to any questions that may arise concerning this submission.

Sincerely,

BERLEX LABORATORIES, INC.



Gerri A. Besta  
Manager, Regulatory Submissions  
and Information  
Drug Regulatory Affairs

Enclosures

GAB\patl\030  
clmintt.doc

ORIGINAL

**BERLEX**

TELEFAX  
CERTIFIED MAIL  
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NDA SUPP AMEND

205-009

BL

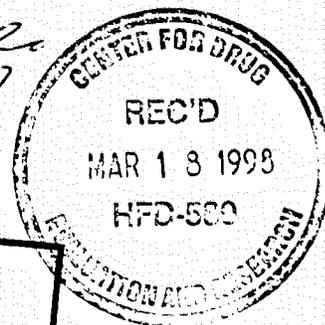
Drug Development & Technology  
Division of Berlex Laboratories, Inc.

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

March 12, 1998

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

*Noted  
for comment  
3/5/98*



REVIEWS COMPLETED		
CSO ACTION:		
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<i>DR</i>	<i>3/25/98</i>	
CSO INITIALS		DATE

*Rev. 2  
copy into fax  
copy  
Hait. 7/11  
3/20/98*

Re: **NDA 20-375**  
**Climara® (estradiol transdermal system)**  
**Amendment to Supplement 009: Intermediate Strength Patch**  
**Response to FDA Request for Information**

Dear Dr. Rarick:

Reference is made to our NDA 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994 and was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995. The NDA provides for two patch sizes, 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup>.

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*Noted  
KR  
3/31/98*

Climara® (estradiol transdermal system)

March 12, 1998

Page 2

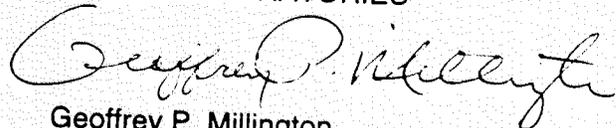
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Attached are two copies of the corrected page of the draft labeling. The correction, under the heading "Description", is an addition of "5.85" which represents the estradiol content in mg for the intermediate strength patch.

Please contact the undersigned at (973) 276-2254 if you have any questions concerning this supplement.

Sincerely,

BERLEX LABORATORIES



Geoffrey P. Millington  
Manager  
Drug Regulatory Affairs

Desk Copy: Ms. Diane Moore

GPM/letter/clima025

# APPROVED

MAR 03 1998

## PRESCRIBING INFORMATION

Climara® estradiol transdermal system

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

### 2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

## DESCRIPTION

Climara®, estradiol transdermal system, is designed to release 17 $\beta$ -estradiol continuously upon application to intact skin. Three (12.5, 18.75 and 25.0 cm<sup>2</sup>) systems are available to provide nominal *in vivo* delivery of 0.05, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 12.5, 18.75 or 25.0 sq cm, and contains 3.9, 5.85 or 7.8 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

Estradiol USP (17 $\beta$ -estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17 $\beta$ -diol. It has an empirical formula of C<sub>18</sub>H<sub>24</sub>O<sub>2</sub> and molecular weight of 272.37. The structural formula is:

The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.

# BERLEX

ORIGINAL

TELEFAX  
CERTIFIED MAIL  
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NDA SUPP AMEND.

500-209  
BB

Drug Development & Technology  
Division of Berlex Laboratories, Inc.

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

REVIEWS COMPLETED

CSO ACTION:

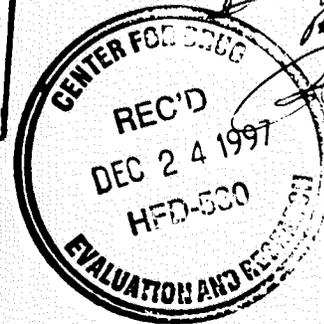
LETTER  N.A.I.  MEMO

CSO INITIALS DATE

*AP* *3/23/98*

December 19, 1997

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



*Noted for Graphon Review*  
*[Signature]*  
*1/5/98*

Re: **NDA 20-375**  
**Climara® (estradiol transdermal system)**  
**Supplement 009: Waiver Request -**  
**Response to FDA Request for Information**

*noted*  
*Ant. 1/11*  
*1-5-98*  
*Reviewed*  
*[Signature]* 2/23/98

Dear Dr. Rarick:

Reference is made to our approved NDA 20-375 for Climara® (estradiol transdermal system) which was approved on December 22, 1994 and was transferred to Berlex Laboratories, Inc. from 3M Pharmaceuticals on November 2, 1995. The NDA provides for two patch sizes, 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup>.

We refer to the supplement submitted on September 19, 1997 which supports a 18.75 cm<sup>2</sup> intermediate patch size. This intermediate size patch is identical in all respects to the approved 12.5 cm<sup>2</sup> and 25 cm<sup>2</sup> patch sizes. The only difference is in the surface area of the patch which is cut with a different size die. The roll stock for the 3 patch sizes is the same.

Climara® (estradiol transdermal system)  
December 19, 1997  
Page 2

The documentation to support this additional patch size was provided in the amendment submitted by 3M Pharmaceuticals to their DMF on September 18, 1997. Enclosed is a copy of the DMF amendment cover letter which authorizes the Division to review this amendment in association with this supplemental application

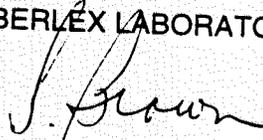
Finally, reference is made to telephone communications between your representative, Ms. Diane Moore and the undersigned on November 24, and December 15, 1997. In these conversations, Ms. Moore requested that Berlex submit a bioavailability waiver based on in vitro release data.

Pursuant to 21 CFR 320.22(d)(2), Berlex is attaching a waiver which includes the in vitro release data for the 18.75 cm<sup>2</sup> patch size. The waiver is based on similar dissolution profiles and dose proportionality of the estradiol pharmacokinetics from the drug product.

Please contact the undersigned at (973) 276-2162 if you have any questions concerning this supplement.

Sincerely,

BERLEX LABORATORIES



Sharon W. Brown  
Associate Director  
Drug Regulatory Affairs

Desk Copy: Ms. Diane Moore

SB/letter/clima186