DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Nancy Konnerth
BERLEX Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045

RE: NDA 20-375
Climara (estradiol transdermal system)
MACMIS #11026

Dear Ms. Konnerth:

We refer to BERLEX Laboratories' (BERLEX) submissions of promotional materials under cover of Form FDA 2253 for Climara (estradiol transdermal system), dated June 14, 2002 and April 15, 2002. These submissions included a professional journal ad, identified as #22-440-0144, and a professional exhibit panel, identified as #22-AD-VERT. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objection follows:

Promotion of Unsubstantiated Claims

Promotional materials are misleading if they state or suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. 21 CFR §202.1(e)(6)(i). Your journal ad and professional exhibit panel are misleading because they present claims for Climara that are not supported by substantial evidence or substantial clinical experience. The approved product labeling (PI) for Climara states that Climara is indicated for "(1) Treatment of moderate to severe vasomotor symptoms associated with the menopause. (2) Treatment of vulvar and vaginal atrophy. (3) Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. (4) Prevention of postmenopausal osteoporosis...."

Your headline "Transdermal ERT - Recommended for the millions of patients with hypertension, hypertriglyceridemia, or gallstones" is misleading because it suggests that Climara has been demonstrated to be useful for patients with hypertension, hypertriglyceridemia, or gallstones, when such has not been demonstrated by substantial evidence or substantial clinical experience. FDA has examined the AACE Guidelines and NAMS "Consensus Opinion" referenced in the journal ad and exhibit panel, and has concluded that they do not constitute substantial evidence or substantial clinical experience,

as required by the regulations, to support claims promoting the use of Climara in patients with hypertension, hypertriglyceridemia, or gallstones. Specifically, because these documents are not based on data from adequate and well-controlled clinical trials studying Climara's use in these patient populations, they do not support your claims.

Furthermore, your claims about these unproven uses are additionally misleading because they mischaracterize what is stated in these referenced documents. Specifically, neither the AACE Guidelines nor the NAMS Consensus Opinion "recommend" the use of your drug in these patient populations. Rather, these documents discuss general considerations and theories as to whether transdermal estrogen replacement therapy or oral estrogen replacement therapy may be preferred for certain patients.

The AACE Guidelines discuss a pharmacokinetic rationale, rather than clinical evidence, for using transdermal estrogen in certain situations, namely, that "the high concentrations of estrogen delivered to the liver by the oral route (in comparison with transdermal absorption directly into the peripheral circulation) induce increased synthesis of triglycerides and certain proteins such as cortisol-binding globulin (transcortin), sex hormone-binding globulin, and angiotensinogen." Similarly, the NAMS Consensus Opinion discusses potential advantages and risks/disadvantages of transdermal estrogen compared with the oral route of administration in women with type 2 diabetes mellitus, such as effects on serum triglyceride levels, alterations in blood pressure, the potential sacrifice of benefits on fibrinolysis, vascular reactivity and/or lipid levels, tolerability issues (such as skin irritation) and expense of therapy. According to this discussion, some of these considerations would argue against using transdermal estrogen replacement therapy.

In summary, contrary to what is suggested in your promotion, the use of transdermal estrogen replacement therapy has not been demonstrated to be safe and effective by the requisite clinical evidence in the specific patient populations referenced in your promotion and is not "recommended" as therapy for these patients by the AACE guidelines and NAMS Consensus Opinion.

Moreover, your promotion of Climara for patients with gallstones and hypertriglyceridemia is particularly troublesome in light of the Warnings section of the PI which states that "A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported," and the Precautions section of the PI which states that "In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications."

Requested Actions

In order to address these violations, we request that you immediately cease the dissemination of this violative professional journal ad, exhibit panel, and all promotional materials that contain the same or similar messages.

Please respond in writing to us within ten business days of the date on this letter. Your response should include your intent to comply with the above request, a list of all violative promotional materials with the same or similar messages, and your methods for discontinuing their use.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 8B-45; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS #11026 and NDA 20-375.

Sincerely,

{See appended electronic signature page}

Sonny Saini, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

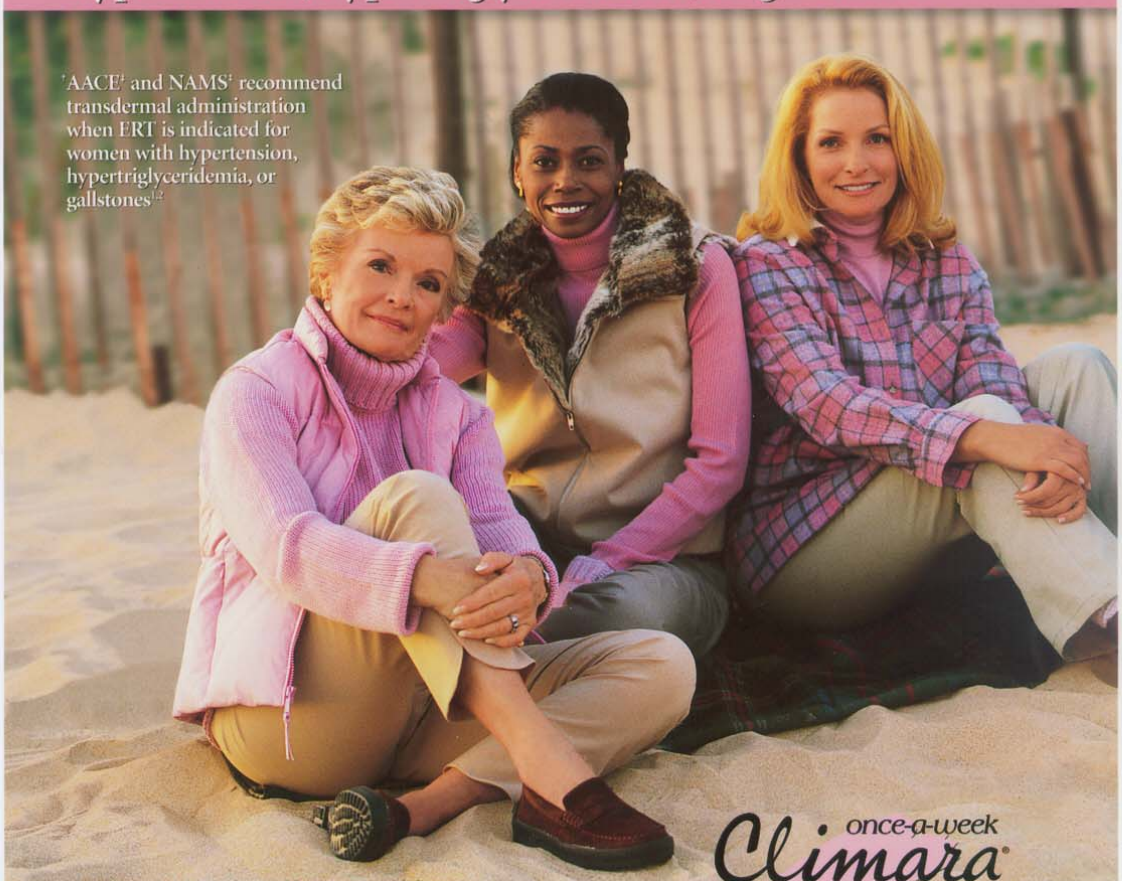
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sonny Saini
1/6/03 03:51:21 PM

Transdermal ERT–

Recommended for the millions of patients with hypertension, hypertriglyceridemia, or gallstones†



†AACE[1] and NAMS[2] recommend transdermal administration when ERT is indicated for women with hypertension, hypertriglyceridemia, or gallstones[1,2]

Estrogens should not be used by patients with known or suspected pregnancy, breast cancer, estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding, active thrombophlebitis, or thromboembolic disorders. Estrogens have been reported to increase the risk of endometrial carcinoma.

Please see full prescribing information available at this exhibit before prescribing or administering.

†AACE = American Association of Clinical Endocrinologists;
NAMS = North American Menopause Society

1. American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. *Endocr Prac*.1999;5(6):355-366.
2. Consensus Opinion. Effects of menopause and estrogen replacement therapy or hormone replacement therapy in women with diabetes mellitus: consensus opinion of the North American Menopause Society. *Menopause*. 2000;7(2):87-95.

once-a-week

Climara®

(estradiol transdermal system)*

0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

*3M Pharmaceuticals/Drug Delivery Systems

Proven protection. Clear convenience.

Visit our website at
www.clearlyclimara.com

BERLEX® Berlex Laboratories, Inc., Montville, NJ 07045

 22-AD-VERT April 2002

Rx only

Climara® (estradiol transdermal system)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see full Prescribing Information.

1. ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER. 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 the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen doses.

2. 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.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see **PRECAUTIONS**). Estrogens may cause fetal harm when administered to a pregnant woman.

2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.

4. Known or suspected estrogen-dependent neoplasia.

5. Active thrombophlebitis or thromboembolic disorders.

6. Climara® should not be used in patients hypersensitive to its ingredients.

WARNINGS

1. **Induction of malignant neoplasms.**

a. Endometrial Cancer.

The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

b. Breast Cancer.

While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen-alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a health-care provider and perform monthly self-breast examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. **Thromboembolic disorders**. The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported in women receiving postmenopausal estrogens.

Cardiovascular disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

3. **Gallbladder disease.** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

4. **Hypercalcemia**. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. **Addition of a progestin when a woman has not had a hysterectomy**. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include: (a) adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and (b) impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. **Cardiovascular risk**. The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in post-menopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. **Elevated blood pressure**. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

4. **Familial hyperlipoproteinemia**. In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

5. **Impaired liver function.** Estrogens may be poorly metabolized in patients with impaired liver function.

6. **Hypothyroidism.** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy, however, may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.

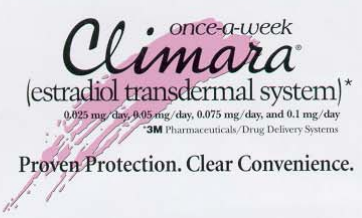
7. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

8. **Exacerbation of endometriosis**. Endometriosis may be exacerbated with administration of estrogen therapy.

9. **Hypocalcemia.** Estrogens should be used with caution in individuals with severe hypocalcemia.

B. Patient Information. See text of Patient Information after the **HOW SUPPLIED** section.

C. Laboratory Tests. Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.



D. Drug/Laboratory Test Interactions.

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, And Impairment Of Fertility. See **CONTRAINDICATIONS**. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy Category X. Climara® should not be used during pregnancy. See **CONTRAINDICATIONS**.

G. Nursing Mothers. The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use. Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

I. Geriatric Use. There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing Climara® to determine whether those over 65 years of age differ from younger subjects in their response to Climara®.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

See **WARNINGS** regarding induction of neoplasia, increased incidence of gallbladder disease, cardiovascular disease, and hypercalcemia; see **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

The most commonly reported adverse reaction to the Climara® system in clinical trials was skin irritation at the application site. In two well-controlled clinical studies, the overall rate of discontinuation due to skin irritation at the application site was 6.8%: 7.9% for the 12.5 cm^2 system and 5.3% for the 25.0 cm^2 system compared with 11.5% for the placebo system. Patients with known skin irritation to the patch were excluded from participation in the studies. The following additional adverse reactions have been reported with estrogen therapy:

Summary of Most Frequently Reported Adverse Experiences/Medical Events (≥5%) by Treatment Groups

	Climara®			
AE per Body System	**0.025 mg/day (N=219)**	**0.05 mg/day (N=201)**	**0.1 mg/day (N=194)**	**Placebo (N=72)**
Body as a Whole	21%	39%	37%	29%
Headache	5%	18%	13%	10%
Pain	1%	8%	11%	7%
Back Pain	4%	8%	9%	6%
Edema	0.5%	13%	10%	6%
Gastro-Intestinal	9%	21%	29%	18%
Abdominal Pain	0.0%	11%	16%	8%
Nausea	1%	5%	6%	3%
Flatulence	1%	3%	7%	1%
Musculo-Skeletal	7%	9%	11%	4%
Arthralgia	1%	5%	5%	3%
Psychiatric	13%	10%	11%	1%
Depression	1%	5%	8%	0%
Reproductive	12%	18%	41%	11%
Breast Pain	5%	8%	29%	4%
Leukorrhea	1%	6%	7%	1%
Respiratory	15%	26%	29%	14%
URTI	6%	17%	17%	8%
Pharyngitis	0.5%	3%	7%	3%
Sinusitis	4%	4%	5%	3%
Rhinitis	2%	4%	6%	1%
Skin and Appendages	19%	12%	12%	15%
Pruritus	0.5%	6%	3%	6%

The following adverse events have been reported spontaneously in association with Climara® use.

1. **Genitourinary system.** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting. Vaginal candidiasis. Changed amount of cervical secretion.
2. **Breasts.** Tenderness, enlargement.
3. **Gastrointestinal.** Nausea, vomiting. Abdominal cramps, bloating.
4. **Skin.** Chloasma or melasma that may persist when drug is discontinued. Loss of scalp hair, hirsutism.
5. **Eyes.** Steepening of corneal curvature. Intolerance of contact lenses.
6. **Central nervous system.** Headache, migraine, dizziness. Mental depression.
7. **Miscellaneous.** Increase or decrease in weight. Changes in libido. Muscle cramps.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

HOW SUPPLIED

Climara® (estradiol transdermal system), 0.025 mg/day – each 6.5 cm^2 system contains 2.0 mg of estradiol USP NDC 50419-454-04

Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.05 mg/day – each 12.5 cm^2 system contains 3.8 mg of estradiol USP NDC 50419-451-04

Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.075 mg/day – each 18.75 cm^2 system contains 5.7 mg of estradiol USP NDC 50419-453-04

Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Climara® (estradiol transdermal system), 0.1 mg/day – each 25.0 cm^2 system contains 7.6 mg of estradiol USP NDC 50419-452-04

Individual Carton of 4 systems
Shelf Pack Carton of 6 Individual Cartons of 4 systems

Do not store above 86° F (30° C). Do not store unpouched.
Apply immediately upon removal from the protective pouch.

Manufactured for Berlex Laboratories, Wayne, NJ 07470
Manufactured by 3M Pharmaceuticals, St. Paul, MN 55144 June 2001

Berlex Component Code #6066302 (3M #672800)

References:

1. American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause. *Endocr Prac.* 1999;5(6):355–366.

2. Consensus Opinion. Effects of menopause and estrogen replacement therapy or hormone replacement therapy in women with diabetes mellitus: consensus opinion of the North American Menopause Society. *Menopause.* 2000;7(2):87–95.

Berlex Laboratories, Inc., Montville, NJ 07045

22-440-0144

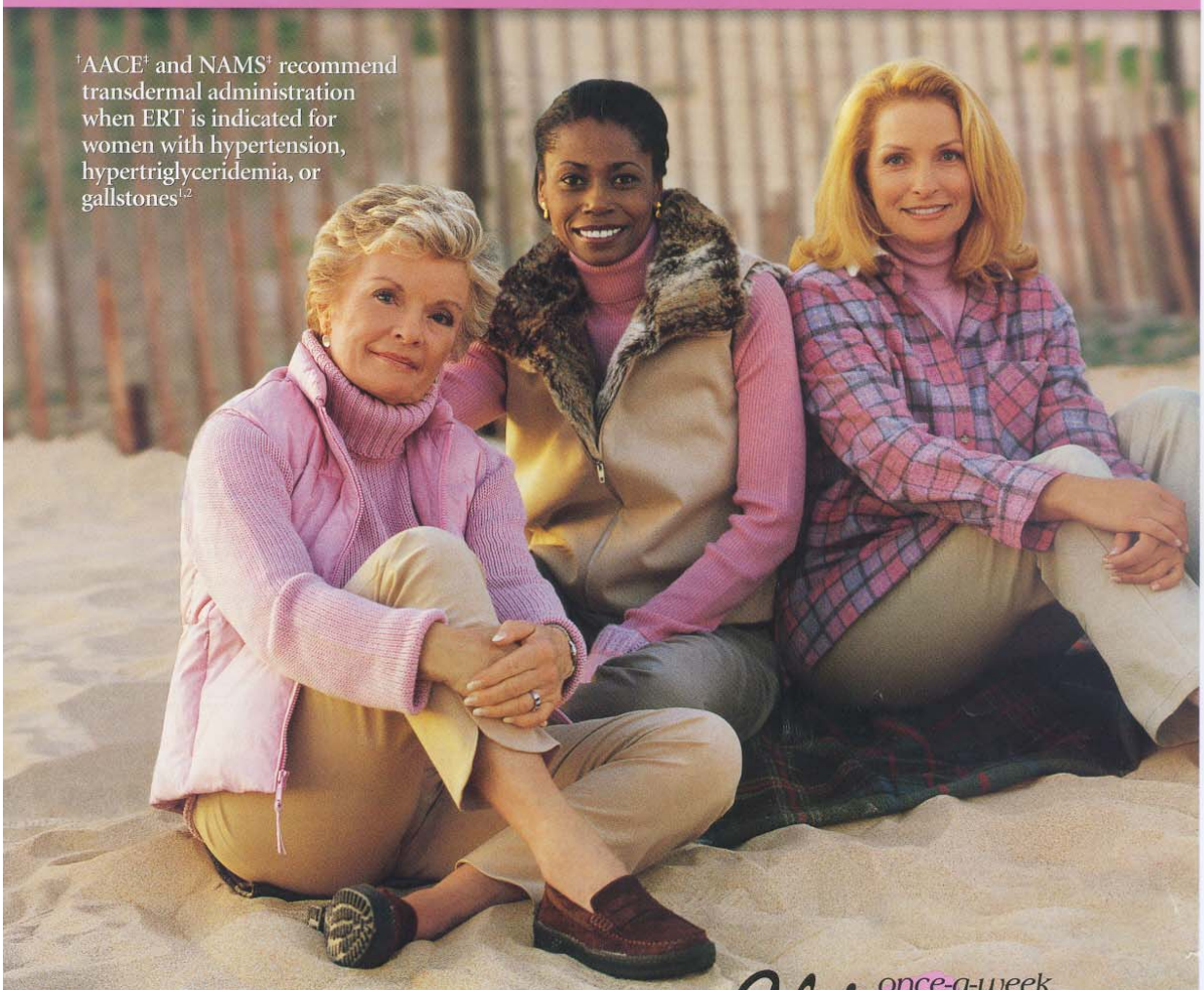
Printed in USA

BERLEX®

May 2002

Transdermal ERT–

Recommended for the millions of patients with hypertension, hypertriglyceridemia, or gallstones†



†AACE‡ and NAMS‡ recommend transdermal administration when ERT is indicated for women with hypertension, hypertriglyceridemia, or gallstones[1,2]

Estrogens should not be used by patients with known or suspected pregnancy, breast cancer, estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding, active thrombophlebitis, or thromboembolic disorders. Estrogens have been reported to increase the risk of endometrial carcinoma.

Please see following page for brief summary of Prescribing Information.

‡AACE = American Association of Clinical Endocrinologists;
NAMS = North American Menopause Society

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22-440-0144 Printed in USA May 2002